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The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. Patent application No. Demande de brevet n°

02292074.8

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk

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AstraZeneca AB

151 85 Södertälje
SUEDE

Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se referer à la description.)

Chemical compounds

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CHEMICAL COMPOUNDS

The present invention relates to compounds which are antagonists of gonadotropin releasing hormone (GnRH) activity. The invention also relates to pharmaceutical formulations, the use of a compound of the present invention in the manufacture of a medicament, a method of therapeutic treatment using such a compound and processes for producing the compounds.

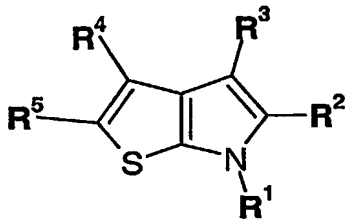
Gonadotropin releasing hormone (GnRH) is a decapeptide that is secreted by the hypothalamus into the hypophyseal portal circulation in response to neural and/or chemical stimuli, causing the biosynthesis and release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) by the pituitary. GnRH is also known by other names, including gonadoliberin, LH releasing hormone (LHRH), FSH releasing hormone (FSH RH) and LH/FSH releasing factor (LH/FSH RF).

GnRH plays an important role in regulating the action of LH and FSH (by regulation of their levels), and thus has a role in regulating the levels of gonadal steroids in both sexes, including the sex hormones progesterone, oestrogens and androgens. More discussion of GnRH can be found in WO 98/5519 and WO 97/14697, the disclosures of which are incorporated herein by reference.

It is believed that several diseases would benefit from the regulation of GnRH activity, in particular by antagonising such activity. These include sex hormone related conditions such as sex hormone dependent cancer, benign prostatic hypertrophy and myoma of the uterus. Examples of sex hormone dependent cancers are prostatic cancer, uterine cancer, breast cancer and pituitary gonadotrophe adenoma.

The following disclose compounds purported to act as GnRH antagonists: WO 97/21435, WO 97/21703, WO 97/21704, WO 97/21707, WO 55116, WO 98/55119, WO 98/55123, WO 98/55470, WO 98/55479, WO 99/21553, WO 99/21557, WO 99/41251, WO 99/41252, WO 00/04013, WO 00/69433, WO 99/51231, WO 99/51232, WO 99/51233, WO 99/51234, WO 99/51595, WO 99/51596, WO 00/53178, WO 00/53180, WO 00/53179, WO 00/53181, WO 00/53185 and WO 00/53602.

It would be desirable to provide further compounds, such compounds being GnRH antagonists. Thus, according to the first aspect of the invention there is provided a compound of Formula (I),



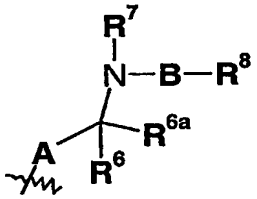
Formula (I)

wherein:

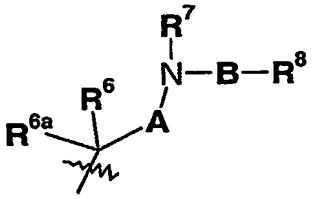
R^1 is selected from: hydrogen, optionally-substituted C_{1-6}alkyl, optionally substituted C_{1-6}alkanoyl, optionally substituted aryl or optionally-substituted arylC_{1-6}alkyl;

R^2 is an optionally-substituted mono or bi-cyclic aromatic ring;

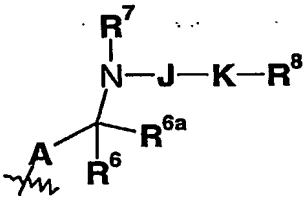
R^3 is selected from a group of Formula (IIa) to Formula (IIf):



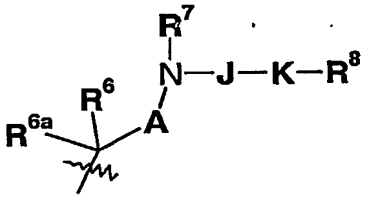
Formula (IIa)



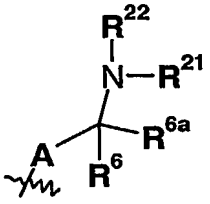
Formula (IIb)



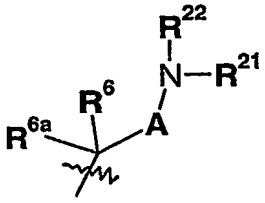
Formula (IIc)



Formula (IId)



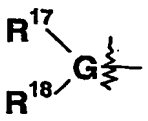
Formula (IIe)



Formula (IIf)

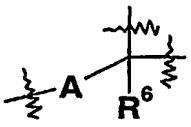
R^4 is selected from: hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted aryl, C_{1-3}perfluoroalkyl, cyano, nitro, halo, $R^9O(CH_2)_m$-, $R^9C(O)N(R^{10})$-, $R^9R^{10}NC(O)N(R^{10})$-, $R^9S(O_n)$- or or $R^9R^{10}NC(O)$-$(CR^9R^{10})_t$-;

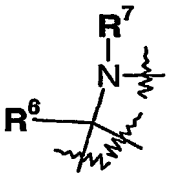
R^5 is a group of Formula (III):



Formula (III)

R^6 and R^{6a} are independently selected from hydrogen, optionally substituted C_{1-6}alkyl, optionally-substituted aryl or optionally substituted arylC_{1-6}alkyl, or R^6 and R^{6a} taken together and the carbon atom to which they are attached form a carbocyclic ring of 3-7 atoms, or R^6 and R^{6a} taken together and the carbon atom to which they are attached form a carbonyl group;

or when **A** is not a direct bond the group  forms a carbocyclic ring of 3-7 carbon atoms or a heterocyclic ring containing one or more heteroatoms;

or the group  forms a heterocyclic ring containing 3-7 carbon atoms and one or more heteroatoms;

R^7 is selected from: hydrogen, optionally-substituted C_{1-6}alkyl, optionally-substituted arylC_{1-6}alkyl, optionally-substituted aryl, optionally substituted heterocyclyl, optionally substituted heterocyclylC_{1-6}alkyl, R^9OC_{1-6}alkyl-, $R^9R^{10}NC_{1-6}$alkyl-, $R^9R^{10}NC(O)C_{1-6}$alkyl, -$C(NR^9R^{10})$=NH;

or when R^3 is a group of Formula (IIc) or (IId) R^7 is of the formula –**J**-**K**-R^8;

R^8 is selected from:

(i) hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, haloC_{1-6}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxy, hydroxyC_{1-6}alkyl, cyano, N-C_{1-4}alkylamino, N,N-di-C_{1-4}alkylamino, C_{1-6}alkyl–$S(O_n)$-, -O-R^b, –NR^bR^c, –C(O)-R^b, –C(O)O-R^b, -$CONR^bR^c$ or NH-C(O)-R^b,

where R^b and R^c are independently selected from hydrogen and C_{1-4}alkyl optionally substituted with hydroxy, amino, N-C_{1-4}alkylamino, N,N-di-C_{1-4}alkylamino, HO-C_{2-4}alkyl-NH- or HO-C_{2-4}alkyl-N(C_{1-4}alkyl)-;

(ii) nitro when **B** is a group of Formula (IV) and **X** is CH and **p** is 0;

(iii) C_{3-7}cycloalkyl, aryl or arylC_{1-6}alkyl each of which is optionally substituted by R^{12}, R^{13} and R^{14};

(iv) -(Q)-aryl , -(Q)-heterocyclyl, -aryl-(Q)-aryl, each of which is optionally substituted by R^{12}, R^{13} and R^{14}

wherein -(Q)- is selected from E, F or a direct bond;

(v) heterocyclyl or heterocyclylC_{1-6}alkyl each of which is optionally substituted by R^{12}, R^{13} and R^{14};

(vi) a group selected from R^{12}, R^{13} and R^{14};

R^9 and R^{10} are independently selected from: hydrogen, hydroxy, optionally substituted C_{1-6}alkyl, optionally substituted aryl, optionally substituted arylC_{1-6}alkyl, an optionally substituted carbocyclic ring of 3-7 atoms, optionally substituted heterocyclyl, optionally substituted heterocyclylC_{1-6}alkyl or R^9 and R^{10} taken together can form an optionally substituted ring of 3-9 atoms or R^9 and R^{10} taken together with the carbon atom to which they are attached form a carbonyl group;

R^{11} is selected from: hydrogen, optionally substituted C_{1-6}alkyl, or $N(R^9R^{10})$;

R^{12} is selected from: hydrogen, hydroxy, $R^{17}R^{18}N$-, optionally substituted C_{1-6}alkyl-$SO_2N(R^9)$-, optionally substituted aryl-$SO_2N(R^9)$-, C_{1-3}perfluoroalkyl-$SO_2N(R^9)$-; optionally substituted C_{1-6}alkyl-$N(R^9)SO_2$-, optionally substituted aryl-$N(R^9)SO_2$-, C_{1-3}perfluoroalkyl-$N(R^9)SO_2$- optionally substituted C_{1-6}alkanoyl-$N(R^9)SO_2$-; optionally substituted aryl-$C(O)N(R^9)SO_2$-, optionally substituted C_{1-6}alkyl-$S(O_n)$ -, optionally substituted aryl-$S(O_n)$ - , C_{1-3}perfluoroalkyl-, C_{1-3}perfluoroalkoxy, optionally substituted C_{1-6}alkoxy, carboxy, halo, nitro or cyano;

R^{13} and R^{14} are independently selected from: hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted C_{2-6}alkenyl, cyano, nitro, C_{1-3}perfluoroalkyl-, C_{1-3}perfluoroalkoxy, optionally substituted aryl, optionally substituted arylC_{1-6}alkyl, $R^9O(CH_2)_s$-, $R^9(O)O(CH_2)_s$-, $R^9OC(O)(CH_2)_s$-, $R^{16}S(O_n)(CH_2)_s$-, $R^9R^{10}NC(O)(CH_2)_s$- or halo;

R^{15} is selected from: hydrogen, optionally substituted C_{1-6}alkyl, $R^{19}OC(O)$-, $R^9R^{10}NC(O)$-, $R^9C(O)$-, $R^9S(O_n)$-;

R^{16} is selected from: hydrogen, C_{1-6}alkyl, C_{1-3}perfluoroalkyl or optionally-substituted aryl;

R^{17} is independently selected from: hydrogen, hydroxy, cyano or optionally substituted C_{1-6}alkyl;

R^{18} is a group of formula R^{18a}-$C(R^9R^{10})_{0-1}$- wherein R^{18a} is selected from: $R^{19}OC(O)$-, $R^9R^{10}NC(O)$-, $R^9R^{10}N$-, $R^9C(O)$-, $R^9C(O)N(R^{10})$-, $R^9R^{10}NC(O)$-, $R^9R^{10}NC(O)N(R^{10})$-, $R^9SO_2N(R^{10})$-, $R^9R^{10}NSO_2N(R^{10})$-, $R^9C(O)O$-, $R^9OC(O)$-, $R^9R^{10}NC(O)O$-, R^9O-,

$R^9S(O_n)$-, $R^9R^{10}NS(O_n)$ -, optionally substituted C_{1-6}alkyl, optionally substituted heterocyclyl;

or R^{17} and R^{18} when taken together form an optionally substituted carbocyclic ring of 3-7 atoms or optionally substituted heterocyclyl;

R^{19} is selected from: hydrogen, optionally substituted C_{1-6}alky, optionally substituted aryl, optionally substituted arylC_{1-6}alkyl, optionally substituted C_{3-7}cycloalkyl, optionally substituted heterocyclyl or optionally substituted heterocyclylC_{1-6}alkyl;

R^{20} is selected from R^{12} or R^{13};

R^{21} and R^{22} are independently selected from hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-7}cycloalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylC_{1-6}alkyl, optionally substituted C_{3-6}alkenyl, optionally substituted C_{3-6}alkynyl, -$(C_{1-6}alkyl)_{aa}$-$S(O_n)$-$(C_{1-5}alkyl)_{bb}$-; $R^9R^{10}NC_{2-6}$alkyl, R^9OC_{2-6}alkyl or $R^9R^{10}NC(O)C_{2-6}$alkyl, with the proviso that R^9 and R^{10} independently or taken together are not optionally substituted aryl or optionally substituted arylC_{1-6}alkyl; or

R^{21} and R^{22} taken together form an optionally substituted non-aromatic heterocyclic ring;

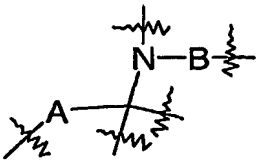
A is selected from:

(i) a direct bond;

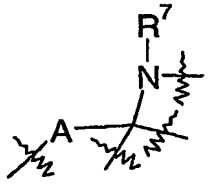
(ii) optionally-substituted C_{1-5}alkylene wherein the optional substituents are independently selected from: optionally-substituted C_{1-6}alkyl optionally-substituted aryl, optionally substituted arylC_{1-6}alkyl or substituted arylC_{1-6}alkyl;

(iii) a carbocyclic ring of 3-7 atoms;

(iv) a carbonyl group;

or when R^3 is a group of Formula (IIa) or (IIb), the group 

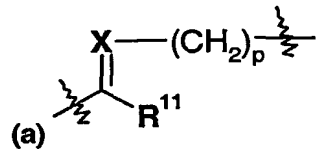
forms a heterocyclic ring containing 3-7 carbon atoms and one or more heteroatoms;

or when R^3 is a group of Formula (IIa), (IIb), (IIc) or (IId), the group  forms a heterocyclic ring containing 3-7 carbon atoms and one or more heteroatoms;

B is selected from:

(i) a direct bond;

(ii) a group of Formula (IV)



Formula (IV)

wherein:

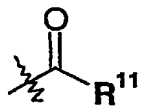
X is selected from N, CH or a saturated heterocyclic ring;

wherein at position (a) Formula (IV) is attached to the nitrogen atom and the $(CH_2)p$ group is attached to R^8; and

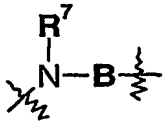
(iii) a group independently selected from: optionally substituted C_{1-6}alkylene, optionally substituted C_{3-7}cycloalkyl, optionally substituted C_{3-6}alkenylene, optionally substituted C_{3-6}alkynyl, C_{1-6}alkoxy, $(C_{1-5}alkyl)_{aa}$-$S(O_n)$-$(C_{1-5}alkyl)_{bb}$-, $(C_{1-5}alkyl)_{aa}$-O-$(C_{1-5}alkyl)_{bb}$- or $(C_{1-5}alkyl)_{aa}$-$N(R^{15})$- $(C_{1-5}alkyl)_{bb}$,

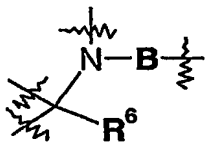
wherein R^{15} and the $(C_{1-5}alkyl)_{aa}$ or $(C_{1-5}alkyl)_{bb}$ chain can be joined to form a ring;

or the group $-B-R^8$ represents a group of Formula (V)



Formula (V);

or the group  together forms a heterocylic ring containing 5-7 carbons atoms;

or the group  forms a heterocyclic ring containing 3-7 carbon atoms and one or more heteroatoms;

E is –O-, -S(O_n), -C(O)-, -NR^{15}- or -C(R^9R^{10})$_q$;

F is -E(CH_2)$_r$- or -(CH_2)$_r$E -;

G is selected from: hydrogen, halo, CN, NO_2, N, O, S(O_n), C(O), C(R^9R^{10})$_t$, optionally substituted C_{2-6}akenylene, optionally substituted C_{2-6}alkynylene, optionally substituted heterocyclyl or a direct bond to R^{18},

J is a group of the formula: -(CH_2)$_s$-**L**-(CH_2)$_s$- wherein when **s** is greater than 0, the alkylene group is optionally substituted

K is selected from: a direct bond, -O-(CH_2)$_s$-, -C(O)-(CH_2)$_s$- , -S(O_n) -(CH_2)$_s$-, -N(R^{18})-(CH_2)$_s$-, -OC(O)-(CH_2)$_s$-, -C(O)O-(CH_2)$_s$-, -OS(O_n)-(CH_2)$_s$-, or -S(O_n)-O-(CH_2)$_s$-;

L is selected from optionally substituted aryl or optionally substituted heterocyclyl;

n is an integer between 0 and 2;

p is an integer between 0 and 4;

q is an integer between 0 and 4;

r is an integer between 0 and 4;

s is an integer between 0 and 4; and

t is an integer between 0 and 4;

aa and **bb** are independently selected from 0 or 1

with the proviso that

(i) when **G** is hydrogen, halo, CN or NO_2, then R^{17} and R^{18} are both absent;

(ii) when **G** is O, S(O_n), C(O) or C($R^{11}R^{12}$)$_t$ then **G** is substituted by a single group independently selected from the definition of R^{17} or R^{18} and when G is a direct bond to R^{18} then **G** is substituted by a single group selected from R^{18}; and

or a salt, pro-drug or solvate thereof.

According to a further feature of the first aspect of the invention there is provided a pharmaceutical formulation comprising a compound of Formula (I), or salt, pro-drug or solvate thereof, and a pharmaceutically acceptable diluent or carrier.

According to a further feature of the first aspect of the invention there is provided the following uses of a compound of a compound of Formula (I), or salt, pro-drug or solvate thereof:

(a) the use in the manufacture of a medicament for antagonising gonadotropin releasing hormone activity;

(b) the use in the manufacture of a medicament for administration to a patient, for reducing the secretion of luteinizing hormone by the pituitary gland of the patient; and

(c) the use in the manufacture of a medicament for administration to a patient, for therapeutically treating and/or preventing a sex hormone related condition in the patient.

According to a further aspect of the invention there is provided a method of antagonising gonadotropin releasing hormone activity in a patient, comprising administering a compound of Formula (I), or salt, pro-drug or solvate thereof, to a patient.

Whilst pharmaceutically-acceptable salts of compounds of the invention are preferred, other non-pharmaceutically-acceptable salts of compounds of the invention may also be useful, for example in the preparation of pharmaceutically-acceptable salts of compounds of the invention.

In the present specification, unless otherwise indicated, an **alkyl, alkylene, alkenyl** or **alkynyl** moiety may be linear or branched. The term "**alkylene**" refers to the group $-CH_2-$. Thus, C_8 alkylene for example is $-(CH_2)_8-$.

The term **"aryl"** refers to phenyl or naphthyl.

The term **"carbamoyl"** refers to the group $-C(O)NH_2$.

The term **"halo"** refers to fluoro, chloro, bromo or iodo.

The term **"heterocyclyl"** or **"heterocyclic ring"** refers to a 5-10 membered aromatic mono or bicyclic ring or a 5-10 membered saturated or partially saturated mono or bicyclic ring, said aromatic, saturated or partially unsaturated rings containing up to 5 heteroatoms independently selected from nitrogen, oxygen or sulphur, linked via ring carbon atoms or ring nitrogen atoms where a bond from a nitrogen is allowed, for example no bond is possible to the nitrogen of a pyridine ring, but a bond is possible through the 1-nitrogen of a pyrazole ring. Examples of 5- or 6-membered aromatic heterocyclic rings include pyrrolyl, furanyl, imidazolyl, triazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyridinyl, isoxazolyl, oxazolyl, 1,2,4 oxadiazolyl, isothiazolyl, thiazolyl and thienyl. A 9 or 10 membered bicyclic aromatic heterocyclic ring is an aromatic bicyclic ring system comprising a 6-membered ring fused to either a 5 membered ring or another 6 membered ring. Examples of 5/6 and 6/6 bicyclic ring systems include benzofuranyl, benzimidazolyl, benzthiophenyl, benzthiazolyl, benzisothiazolyl, benzoxazolyl, benzisoxazolyl, indolyl, pyridoimidazolyl, pyrimidoimidazolyl, quinolinyl, isoquinolinyl, quinoxalinyl, quinazolinyl, phthalazinyl, cinnolinyl and naphthyridinyl. Examples of saturated or partially saturated heterocyclic rings

include pyrrolinyl, pyrrolidinyl, morpholinyl, piperidinyl, piperazinyl, dihydropyridinyl and dihydropyrimidinyl.

The term **"aromatic ring"** refers to a 5-10 membered aromatic mono or bicyclic ring optionally containing up to 5 heteroatoms independently selected from nitrogen, oxygen or sulphur. Examples of such "aromatic rings" include: phenyl, pyrrolyl, furanyl, imidazolyl, triazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyridinyl, isoxazolyl, oxazolyl, 1,2,4 oxadiazolyl, isothiazolyl, thiazolyl and thienyl. Preferred aromatic rings include 'phenyl, thienyl and pyridyl.

The symbol  denotes where the respective group is linked to the remainder of the molecule.

The term **C_{1-3}perfluoroalkyl** refers to a C_{1-3}alkyl chain in which all hydrogens have been replaced with a fluorine atom. Examples of **C_{1-3}perfluoroalkyl** include trifluromethyl, pentafluoroethyl and 1-trifluoromethyl-1,2,2,2-tetrafluoroethyl-. Preferably **C_{1-3}perfluoroalkyl** is trifluromethyl.

Examples of **C_{1-8}alkyl** include: methyl, ethyl, propyl, isopropyl, butyl, *iso*-butyl, *tert*-butyl and 2-methyl-pentyl; example of **C_{1-8}alkylene** include: methylene, ethylene and 2-methyl-propylene; examples of **C_{1-6}alkenyl** include allyl (2-propenyl) and 2—butenyl, examples of **C_{1-6}alkynyl** 2-propynyl and 3-butynyl, examples of **haloC_{1-6}alkyl** include fluoroethyl, chloropropyl and bromobutyl, examples of **hydroxyC_{1-6}alkyl** include hydroxymethyl, hydroxyethyl and hydroxybutyl, examples of **C_{1-8}alkoxy** include methoxy, ethoxy and butyloxy; examples of **C_{1-4}alkoxyC_{1-4}alkyl** include methoxyethyl, propoxybutyl and propoxymethyl, examples of **C_{1-6}alkanoyl** incude formyl, ethanoyl, propanoyl or pentanoyl, examples of **N-C_{1-4}alkylamino** include N-methylamino and N-ethylamino; examples of **N,N-di-C_{1-4}alkylamino** include N,N-dimethylaminoethyl, N,N-di-methylaminopropyl and N,N-dipropylaminoethyl, examples of **HO-C_{2-4}alkyl-NH** include hydroxymethylamino hydroxyethylamino and hydroxypropyamino, examples of **HO-C_{2-4}alkyl-N(C_{1-4}alkyl)** include N-methyl-hydroxymethylamino, N-ethyl-hydroxyethylamino, and N-propyl-hydroxypropyamino, examples of C_{1-6}alkyl-S(O_n)-methylthio, methylsulphinyl, ethylsulphinyl, ethylsulphonyl and propylsulphonyl, include examples of **arylC_{1-6}alkyl** include benzyl, phenethyl and phenylbutyl, examples of **heterocyclylC_{1-6}alkyl** include pyrrolidin-1-yl ethyl, imidazolylethyl, pyridylmethyl and pyrimidinylethyl.

It is to be understood that, insofar as certain of the compounds of the invention may exist in optically active or racemic forms by virtue of one or more asymmetric carbon atoms, the invention includes in its definition any such optically active or racemic form which possesses the property of antagonizing gonadotropin releasing hormone (GnRH) activity. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form. Similarly, activity of these compounds may be evaluated using the standard laboratory techniques referred to hereinafter.

The invention also relates to any and all tautomeric forms of the compounds of the different features of the invention that possess the property of antagonizing gonadotropin releasing hormone (GnRH) activity.

It will also be understood that certain compounds of the present invention may exist in solvated, for example hydrated, as well as unsolvated forms. It is to be understood that the present invention encompasses all such solvated forms which possess the property of antagonizing gonadotropin releasing hormone (GnRH) activity.

Preferred compounds of Formula (I) are those wherein any one of the following apply.

Preferably $\mathbf{R^1}$ is selected from hydrogen or optionally substituted C_{1-6}alkyl. More preferably $\mathbf{R^1}$ represents hydrogen, methyl, ethyl or *tert*-butyl. Most preferably $\mathbf{R^1}$ represents hydrogen.

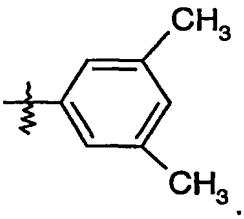
Preferably optional substituents on $\mathbf{R^1}$ are independently selected from: optionally-substituted C_{1-6}alkyl, optionally-substituted C_{2-6}alkenyl, cyano, nitro, C_{1-3}perfluoroalkyl, C_{1-3}perfluoroalkoxy, optionally-substituted aryl, optionally-substituted arylC_{1-6}alkyl, $\mathbf{R^9}O(CH_2)_v$-; $\mathbf{R^9}C(O)O(CH_2)_v$-, $\mathbf{R^9}OC(O)(CH_2)_v$-, $\mathbf{R^{16}}S(O_n)(CH_2)_v$-, $\mathbf{R^9R^{10}}NC(O)(CH_2)_v$-, or halo wherein v is an integer between 0 and 4, and where 2 optional substituents are present together they can optionally form a C_{3-7}carbocyclic ring or a heterocyclic ring.

Preferably $\mathbf{R^2}$ is an optionally substituted monocyclic aromatic ring structure. Most preferably $\mathbf{R^2}$ represents optionally substituted phenyl.

Preferably optional substituents on $\mathbf{R^2}$ are independently selected from: optionally substituted C_{1-6}alkyl, optionally substituted C_{2-6}alkenyl, cyano, nitro, C_{1-3}perfluoroalkyl, C_{1-3}perfluoroalkoxy, optionally substituted aryl, optionally substituted arylC_{1-6}alkyl, $\mathbf{R^9}O(CH_2)_p$-, $\mathbf{R^9}C(O)O(CH_2)_w$-, $\mathbf{R^9}OC(O)(CH_2)_w$-, $\mathbf{R^{16}}S(O_n)(CH_2)_w$-, $\mathbf{R^9R^{10}}NC(O)(CH_2)_w$-, $\mathbf{R^9R^{10}}N$- or halo; wherein w is an integer between 0 and 4 and $\mathbf{R^9}$ and $\mathbf{R^{10}}$ are as defined

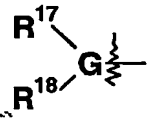
above. Further preferably the optional substituents on R^2 are independently selected from cyano, R^eR^fN-, optionally substituted C_{1-6}alkyl (preferably, C_{1-4}alkyl, eg, methyl or ethyl), optionally substituted C_{1-6}alkoxy (preferably, C_{1-4}alkoxy, eg, methoxy, ethoxy or *tert*-butoxy) or halo (eg, F, Br or Cl) wherein R^e and R^f are independently selected from hydrogen, C_{1-6}alkyl or aryl. Yet further preferably optional substituents on R^2 are independently selected from methyl, ethyl, methoxy, ethoxy, *tert*-butoxy, F or Cl. Most preferably optional substituents on R^2 are independently selected from methyl, F or Cl. Preferably R^2 bears 1, 2 or 3 substituents.

Most preferably R^2 represents



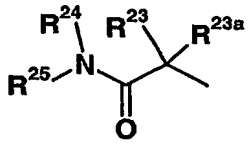
Preferably R^3 is selected from a group of Formula (IIa) or Formula (IIb). Most preferably R^3 is a group of Formula (IIb).

Preferably R^4 is selected from hydrogen or C_{1-4}alkyl. Most preferably R^4 is hydrogen. Preferably the group of Formula (III):

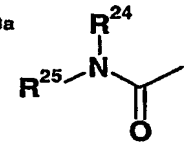


Formula (III)

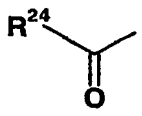
is selected from one of a group of Formula III-a to III-j;



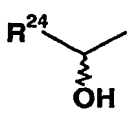
III-a



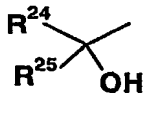
III-b



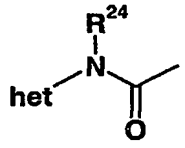
III-c



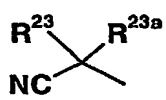
III-d



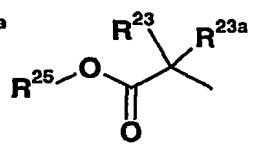
III-e



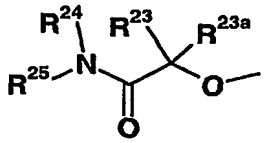
III-f



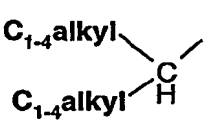
III-g



III-h



III-i



III-j

wherein:

het represents an optionally substituted 3- to 8- membered heterocyclic ring containing from 1 to 4 heteroatoms independently selected from O, N and S;

R^{23} and R^{23a} are independently selected from:

(i) hydrogen or optionally substituted C_{1-8}alkyl; or

(ii) R^{23} and R^{23a} together with the carbon to which they are attached form an optionally substituted 3 to 7-membered cycloalkyl ring;

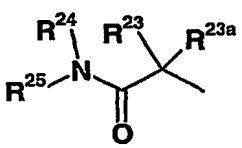
R^{24} and R^{25} are selected from:

(i) R^{24} selected from hydrogen; optionally substituted C_{1-8}alkyl; optionally substituted aryl; -R^{d}-Ar, where R^{d} represents C_{1-8}alkylene and Ar represents optionally substituted aryl; and optionally substituted 3- to 8- membered heterocyclic ring optionally containing from 1 to 3 further heteroatoms independently selected from O, N and S; and R^{25} is selected from hydrogen; optionally substituted C_{1-8}alkyl and optionally substituted aryl;

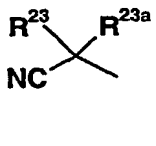
(ii) wherein the group of Formula (III) represents a group of Formula **III-a** , **III-b** or **III-i**, then the group $NR^{24}(-R^{25})$ represents an optionally substituted 3- to 8- membered heterocyclic ring optionally containing from 1 to 3 further heteroatoms independently selected from O, N and S; or

(iii) wherein the group of Formula (III) represents structure **III-e**,  represents an optionally substituted 3- to 8- membered heterocyclic ring optionally containing from 1 to 4 heteroatoms independently selected from O, N and S;

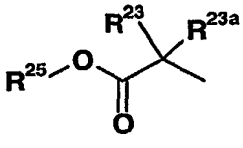
Preferably the group of Formula (III) is selected from a group of Formula **III-a** , **III-g**, **III-h**, or **III-i**:



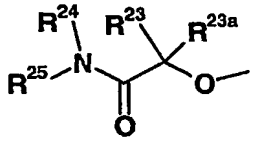
III-a



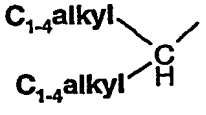
III-g



III-h



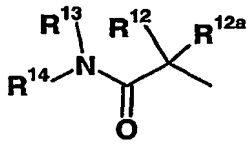
III-i



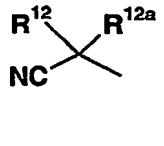
III-j

wherein R^{23}, R^{23a}, R^{24} and R^{25} are as defined above.

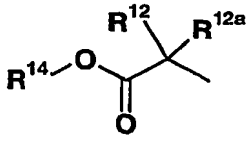
Further preferably the group of Formula (III) is selected from one of the following groups:



III-a



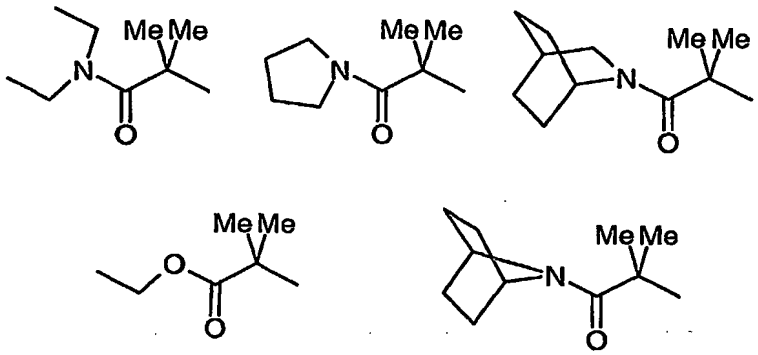
III-g



III-h

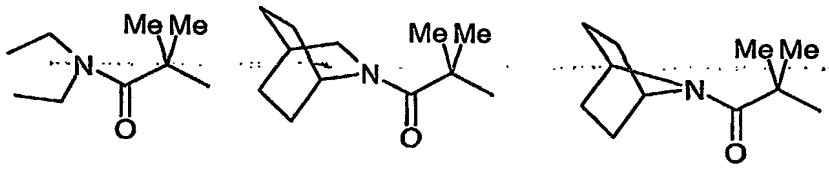
wherein R^{23}, R^{23a}, R^{24} and R^{25} are as defined above.

Yet further preferably the group of Formula (III) is selected from one of the following groups:



wherein Me represents methyl.

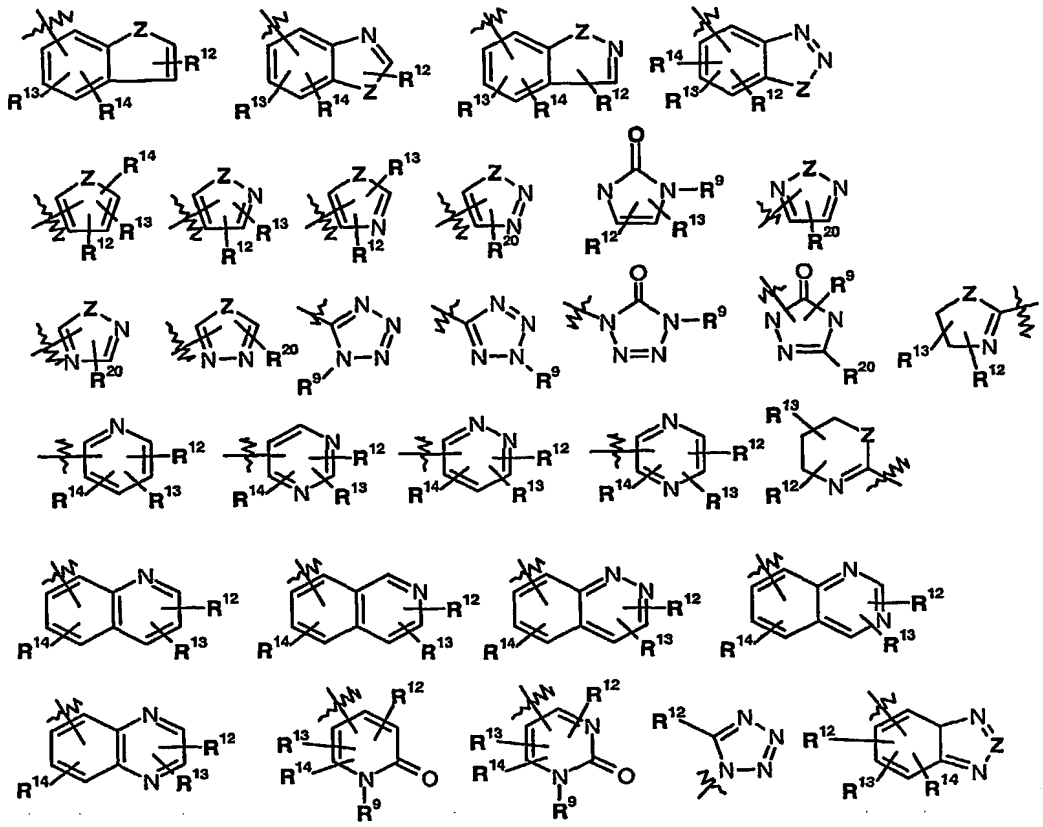
Most preferably the group of Formula (III) is selected from one of the following groups:



Preferably R^6 **and** R^{6a} are independently selected from hydrogen or optionally substituted C_{1-6}alkyl. Preferably independently selected from hydrogen and unsubstituted C_{1-6}alkyl. Most preferably independently selected from hydrogen or methyl.

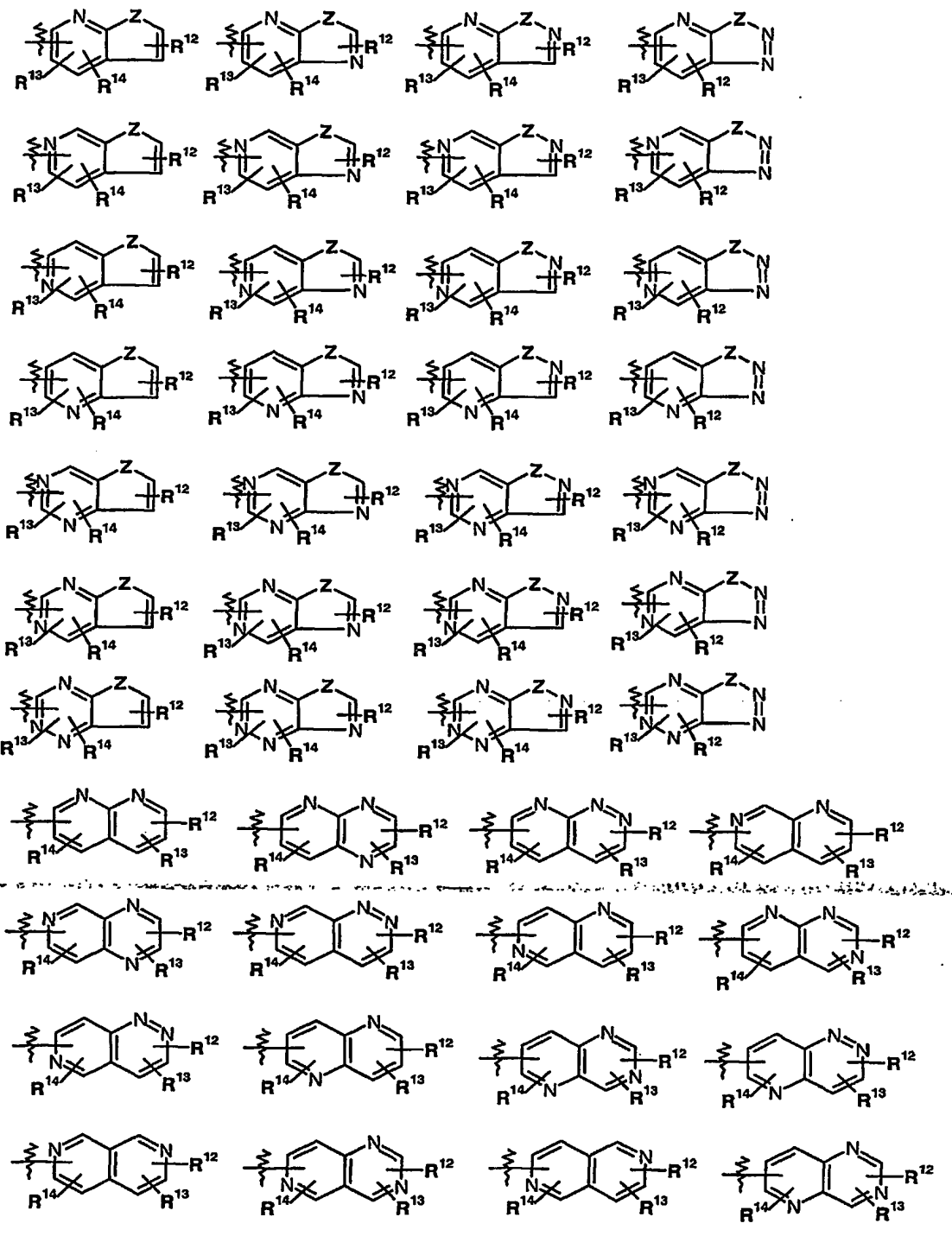
Preferably R^7 is selected from: hydrogen or C_{1-4}alkyl. More preferably R^7 is hydrogen or methyl. Most preferably R^7 is hydrogen.

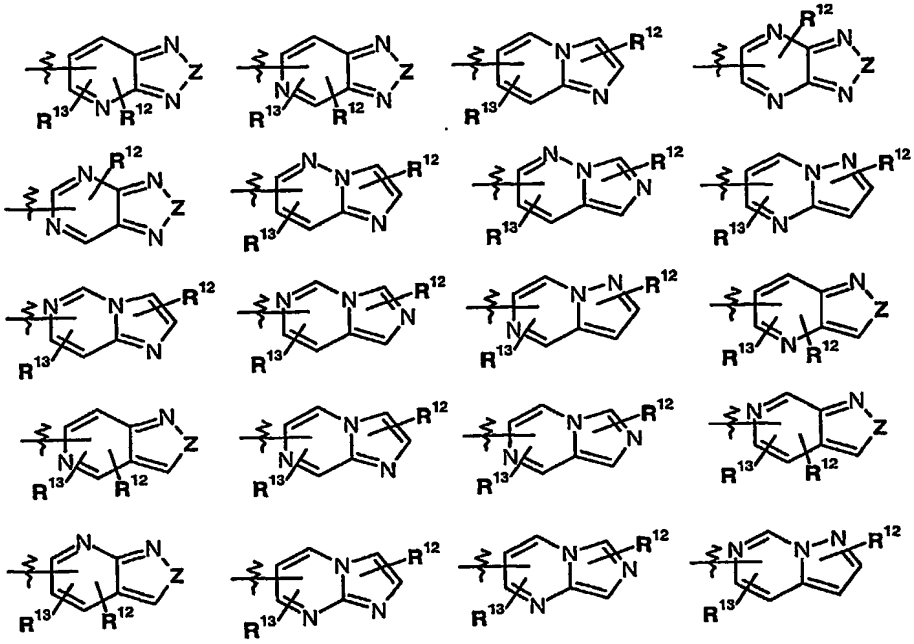
When R^8 is heterocyclyl then R^8 is preferably selected from one of the following groups:



wherein **Z** is selected from: O, S or N($\mathbf{R^9}$), $\mathbf{R^{20}}$ is selected form any group within the definitions of $\mathbf{R^{12}}$ and $\mathbf{R^{13}}$, and $\mathbf{R^9}$, $\mathbf{R^{12}}$, $\mathbf{R^{13}}$ and $\mathbf{R^{14}}$ are as defined above.

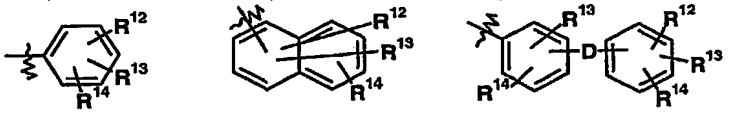
In a further embodiment of the invention when $\mathbf{R^8}$ is heterocyclyl then $\mathbf{R^8}$ is preferably selected from one of the following groups:





wherein **Z** is selected from: O, S or N(R^9) and R^9, R^{12} and R^{13} are as defined above.

When R^8 is aryl or aryl-(**Q**)-aryl optionally substituted by R^{12}, R^{13} and R^{14}, R^8 is preferably selected one of the following groups:



wherein **D** is selected from group **E**, group **F** or a direct bond;

Preferably R^8 is selected from hydrogen, cyano, C_{1-4}alkyl (more preferably methyl), C_{2-6}alkynyl (more prefeably 2-propynyl), hydroxyC_{1-6}alkyl (more preferably hydroxyethyl), C_{1-4}alkoxyC_{1-4}alkyl (more preferably methoxyethyl), haloC_{1-6}alkyl (more preferably fluoroethyl), C_{1-4}alkanoyl (more preferably formyl), C_{1-4}alkoxycarbonyl (more preferably butyloxycarbonyl), N,N-di-C_{1-4}alkylamino (more preferably N,N-dimethylaminoethyl and N,N-dimethylaminopropyl), C_{1-6}alkyl–S(O_n)- (more preferably ethylsulphonyl), cyclopentyl, phenyl, benzyl, cyanophenyl, pyrrolidinyl, pyrrolidinylethyl, imidazolyl, imidazolyC_{1-6}alkyl (more preferably imidazolylethyl), thiazolyl, pyridyl, pyridylC_{1-6}alkyl (more preferably pyridylmethyl) or pyrimidyl wherein a phenyl or heterocyclyl ring is optionally substituted by C_{1-4}alkyl.

When R^9 and/or R^{10} is a component of group **G**, R^9 and R^{10} are preferably independently selected from hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted aryl, optionally substituted arylC_{1-6}alkyl or R^9 and R^{10} forms C_{3-7}cycloalkyl or heterocyclyl.

Further preferably hydrogen or C_{1-4}alkyl. Most preferably hydrogen or methyl. Most preferably both R^9 and R^{10} are methyl.

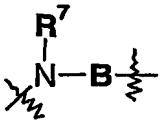
When R^9 and/or R^{10} is a component of group R^{18}, R^9 and R^{10} are preferably independently selected from hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted aryl, optionally substituted arylC_{1-6}alkyl or R^9 and R^{10} forms C_{3-7}cycloalkyl or heterocyclyl. Further preferably hen R^9 is a component of group R^{18}, R^9 is preferably heterocyclyl. Most preferably pyrrolidinyl, 7-azabicyclo[2.2.1]hept-7-yl or. 3-azabicyclo[3.2.2]nonyl.

Preferably R^{17} is hydrogen, hydroxy, cyano or is absent. Most preferably R^{17} is absent.

Preferably R^{18} is selected from hydrogen, $R^9N(R^{10})C(O)$-, $R^9C(O)$-, $R^9OC(O)$- or R^{18a}-$C(R^9R^{10})$- wherein R^{18a} is $R^9N(R^{10})C(O)$-. Further preferably $R^9C(O)$-. Most preferably $R^9C(O)$- wherein R^9 is heterocyclyl..

Preferably A is selected from optionally substituted C_{1-5}alkylene. Further preferably C_{1-5}alkylene optionally substituted with C_{1-4}alkyl. Yet further preferably unsubstituted C_{1-2}alkylene. Most preferably methylene.

Preferably B is selected from optionally substituted C_{1-6}alkylene or the group



forms a C_{5-7}heterocyclic ring. Preferably unsubstituted C_{-6}alkylene or a C_{5-7}heterocyclic saturated ring. Most preferably methylene, ethylene, propylene, butylene or piperazinyl.

Peferably G is a direct bond, -O- or $-C(R^9R^{10})$-. More preferably $-C(R^9R^{10})$-. Most preferably $-C(CH_3)_2$-

Preferably optional substituents on heterocyclyl groups in R^8, R^9, R^{10}, R^{18} and R^{19} or on heterocyclyl groups formed when R^{17} and R^{18} together form a heterocyclic ring are selected from: optionally substituted C_{1-6}alkyl, C_{1-6}alkoxy, optionally substituted C_{2-6}alkenyl, cyano, nitro, C_{1-3}perfluoroalkyl, C_{1-3}perfluoroalkoxy, optionally substituted aryl, optionally substituted arylC_{1-6}alkyl, $R^9O(CH_2)_p$-, $R^9C(O)O(CH_2)_w$-, $R^9OC(O)(CH_2)_w$-, $R^{16}S(O_n)(CH_2)_w$-, $R^9R^{10}NC(O)(CH_2)_w$- or halo; wherein w is an integer between 0 and 4 and p, R^9, R^{10} and R^{16} are as defined above.

Preferably the optional substituents on alkyl, alkenyl, alkynyl, cycloalkyl and aryl groups are independently selected from C_{1-6}alkyl, C_{1-6}alkoxy, C_{3-7}cycloalkyl, optionally substituted aryl, optionally substituted arylC_{1-6}alkyl, hydroxy, oxo, cyano, C_{1-6}alkoxy, halo

(preferably fluoro), $R^{16}S(O_n)(CH_2)_w$-, $R^9OC(O)$-, optionally substituted arylC_{1-3}alkoxy wherein R^9 is as defined above.

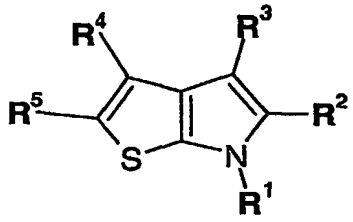
Preferably the optional substituents on optionally substituted aryl and arylC_{1-6}alkyl groups are selected from: optionally substituted C_{1-6}alkyl, optionally substituted C_{2-6}alkenyl, cyano, nitro, halo (preferably fluoro), C_{1-3}perfluoroalkyl, C_{1-3}perfluoroalkoxy, optionally substituted aryl, optionally substituted arylC_{1-6}alkyl, $R^9O(CH_2)_p$-, $R^9C(O)O(CH_2)_w$-, $R^9OC(O)(CH_2)_w$-, $R^{16}S(O_n)(CH_2)_w$-, $R^9R^{10}NC(O)(CH_2)_w$- or halo; wherein w is an integer between 0 and 4 and n, R^9 and R^{10} are as defined above..

In preferences for heterocyclyl in R^8 the nitrogen atoms contained in R^8 heteroaromatic rings exist either as drawn or, where chemically allowed, in their oxidised (N→O, N-OH) state.

Where optional substitution is mentioned at various places the optional substituents also comprise the following definition which refers to one, two, three or more optional substituents. Unless otherwise indicated above (i.e., where a list of optional substituents is specifically listed within a definition), each substituent can be independently selected from C_{1-8}alkyl (eg, C_{2-6}alkyl, and most preferably methyl, ethyl or *tert*-butyl); C_{3-8}cycloalkoxy, preferably cyclopropoxy, cyclobutoxy or cyclopentoxy; C_{1-6}alkoxy, preferably methoxy or C_{2-4}alkoxy; halo, preferably Cl or F; Hal_3C-, Hal_2CH-, $HalCH_2$-, Hal_3CO-, Hal_2CHO or Hal CH_2O, wherein Hal represents halo (preferably F); R^gCH_2O-, $R^hC(O)N(R)$-, $R^hSO_2N(R)$- or R^g-R^hN-; wherein R^g and R^h independently represent hydrogen or C_{1-8}alkyl (preferably methyl or C_{2-6}alkyl or C_{2-4}alkyl), or R^g-R^hN- represents an optionally substituted C_{3-8}, preferably C_{3-6}, heterocyclic ring optionally containing from 1 to 3 further heteroatoms independently selected from O, N and S; hydrogen; or $R^kC(O)O$- or $R^kC(O)$-, R^k representing hydrogen, optionally substituted phenyl or C_{1-6}alkyl (preferably methyl, ethyl, *iso*-propyl or *tert*-butyl). For optional substitution of the heterocyclic ring represented by R^g-R^hN-, at least one (eg, one, two or three) substituents may be provided independently selected from C_{1-6}alkyl (eg, C_{2-4}alkyl, more preferably methyl); phenyl; CF_3O-; F_2CHO-; C_{1-8}alkoxy, preferably methoxy, ethoxy or C_{3-6}alkoxy; C_{1-8}alkoxyC(O), preferably methoxycarbonyl, ethoxycarbonyl, *tert*-butoxycarbonyl or C_{3-6}alkoxyC(O)-; phenoxycarbonyl; phenoxy; C_{1-8}alkanoyl, preferably acetyl, ethanoyl or C_{3-6}alkyanoyl; carboxy; C_{1-8}alkyl$S(O_{nn})$ wherein nn is an integer between 0 and 2, preferably methylthio, ethylthio, C_{3-6}alkylthio, methylsulphinyl, ethylsulphinyl, C_{3-6}alkylsulphinyl, methylsulphonyl, ethylsulphonyl or C_{3-6}alkylsulphonyl; hydroxy; halo (eg, F, Cl or Br); R^mR^nN- where R^m and R^n are

independently hydrogen or C_{1-6}alkyl (preferably C_{2-4}alkyl, more preferably methyl, most preferably R^m=R^n=methyl); and nitro.

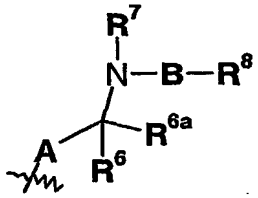
According to a further aspect of the invention there is provided a compound of Formula (Ia)



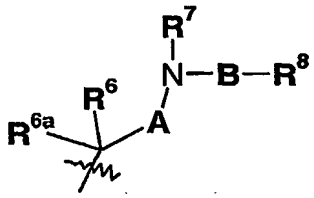
Formula (Ia)

wherein

R^3 is selected from a group of Formula (IIa) or Formula (IIb):



Formula (IIa)



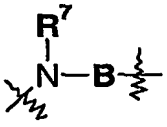
Formula (IIb)

and R^1, R^2, R^4, R^5, R^6, R^{6a}, R^7, R^8, A and B are as defined above;

or salt, solvate or pro-drug thereof.

A further preferred group of compounds of the invention comprises a compound of Formula (Ia), wherein:

A is optionally substituted C_{1-5}alkylene;

B is selected from optionally substituted C_{1-6}alkylene or the group  forms a ring containing C_{5-7}heterocyclic ring;

R^1 is hydrogen or C_{1-4}alkyl;

R^6 and R^{6a}, are independently selected from hydrogen and optionally substituted C_{1-6}alkyl;

R^7 is selected from: hydrogen or C_{1-4}alkyl;

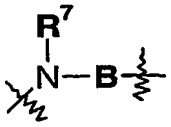
R^8 is selected from hydrogen, cyano, C_{1-6}alkyl, haloC_{1-6}alkyl, C_{2-6}alkynyl, C_{1-6}alkanoyl, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-6}alkoxycarbonyl, N,N-di-C_{1-4}alkylamino, aryl, arylC_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-6}alkyl, heterocyclyl, heterocyclylC_{1-6}alkyl, or heterocyclylcarbonylC_{1-4}alkyl wherein aryl and heterocyclyl rings are optionally substituted by cyano and C_{1-4}alkyl; and

R^2, R^4, and R^5; are as defined above

or salt, solvate or pro-drug thereof.

A further preferred group of compounds of the invention comprises a compound of Formula (Ia), wherein:

A is optionally substituted C_{1-5}alkylene;

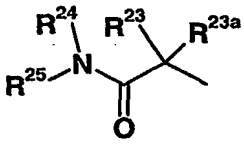
B is selected from optionally substituted C_{1-6}alkylene or the group  forms a ring containing C_{5-7}heterocyclic ring;

R^1 is hydrogen or C_{1-4}alkyl, preferably hydrogen;

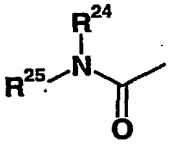
R^2 is an optionally substituted monocyclic aromatic ring structure, preferably optionally substituted phenyl, most preferably 3,5-dimethylphen-1-yl;

R^4 is hydrogen or C_{1-4}alkyl, preferably hydrogen;

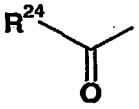
R^5 is a group of Formula (III) wherein the group of Formula (III) is selected from a group of Formula **III-a**; **III-b**; **III-c**; **III-d**; **III-e**; **III-f**, **III-g** , **III-h**, **III-i** or: **III-j**;



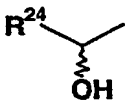
III-a



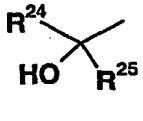
III-b



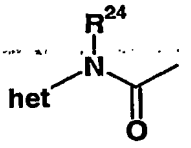
III-c



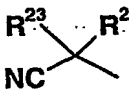
III-d



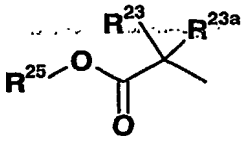
III-e



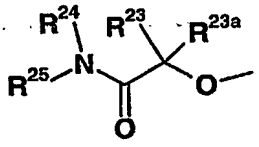
III-f



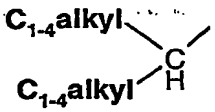
III-g



III-h



III-i



III-j

wherein R^{23}, R^{23a}, R^{24} and R^{25} are as defined above, preferably the group of Formula (III) is selected from (III-a), (III-g) and (III-h);

$R^6$and R^{6a}, are independently selected from hydrogen and optionally substituted C_{1-6}alkyl;

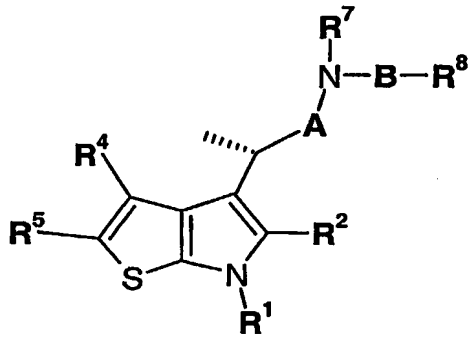
R^7 is selected from: hydrogen or C_{1-4}alkyl;

R^8 is selected from hydrogen, cyano, C_{1-6}alkyl, haloC_{1-6}alkyl, C_{2-6}alkynyl, C_{1-6}alkanoyl, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-6}alkoxycarbonyl, N,N-di-C_{1-4}alkylamino, aryl, arylC_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-6}alkyl, heterocyclyl, heterocyclylC_{1-6}alkyl, or heterocyclylcarbonylC_{1-4}alkyl wherein aryl and heterocyclyl rings are optionally substituted by cyano and C_{1-4}alkyl; and

R^2, R^4, and R^5; are as defined above

or salt, solvate or pro-drug thereof.

A further preferred group of compounds of the invention comprises a compound of Formula (Ib):



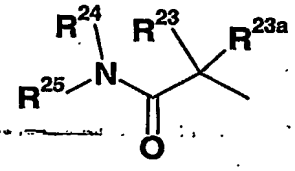
Formula (Ib)

Wherein R^1, R^2, R^4, R^5; R^7, R^8, A and B are as defined above

or salt, solvate or pro-drug thereof.

A yet further preferred group of compounds of the invention comprises a compound of Formula (I), (Ia) or (Ib) wherein:

R^5 is a group of Formula (III) wherein the group of Formula (III) is a group of formula **IIIa**:



IIIa ;

wherein R^{23}, R^{23a}, R^{24} and R^{25} are as defined above;

or a salt, pro-drug or solvate thereof.

According to a further aspect of the invention there is provided a compound of Formula (I), or salt, solvate or pro-drug thereof, wherein R^3 is selected from a group of Formula (IIc) or Formula (IId) and R^1, R^2, R^4 and R^5 are as defined above.

According to a further aspect of the invention there is provided a compound of Formula (I), or salt, solvate or pro-drug thereof, wherein R^3 is selected from a group of Formula (IIe) or Formula (IIf) and R^1, R^2, R^4 and R^5 are as defined above.

According to a further aspect of the invention there is provided a compound of Formula (I), or salt, solvate or pro-drug thereof, wherein R^3 is selected from a group of Formula (IIa), Formula (IIc) or Formula (IIe) and R^1, R^2, R^4 and R^5 are as defined above.

According to a further aspect of the invention there is provided a compound of Formula (I), or salt, solvate or pro-drug thereof, wherein R^3 is selected from a group of Formula (IIb), Formula (IId) or Formula (IIf) and R^1, R^2, R^4 and R^5 are as defined above.

Particularly preferred compounds according to the present invention are wherein the compound is selected from:

N-{2-[2-(1,1-dimethyl-2-oxo-2-pyrrolidin-1-ylethyl)-5-(3,5-dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrol-4-yl]ethyl}-4-pyridin-4-ylbutan-1-amine;

N-{2-[2-[2-(7-azabicyclo[2.2.1]hept-7-yl)-1,1-dimethyl-2-oxoethyl]-5-(3,5-dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrol-4-yl]ethyl}-4-pyridin-4-ylbutan-1-amine;

N-{2-[2-[2-(7-azabicyclo[2.2.1]hept-7-yl)-1,1-dimethyl-2-oxoethyl]-5-(3,5-dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrol-4-yl]ethyl}-4-pyridin-4-ylethyl-1-amine;

{(2*S*)-2-[2-[2-(7-azabicyclo[2.2.1]hept-7-yl)-1,1-dimethyl-2-oxoethyl]-5-(3,5-dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrol-4-yl]propyl}(2-pyridin-4-ylethyl)amine;

N-{2-[2-[2-(2-azabicyclo[2.2.2]oct-2-yl)-1,1-dimethyl-2-oxoethyl]-5-(3,5-dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrol-4-yl]ethyl}-4-pyridin-4-ylbutan-1-amine;

N-{2-[2-[2-(2-azabicyclo[2.2.2]oct-2-yl)-1,1-dimethyl-2-oxoethyl]-5-(3,5-dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrol-4-yl]ethyl}-4-pyridin-4-ylethyl-1-amine;

{(2*S*)-2-[2-[2-(2-azabicyclo[2.2.2]oct-2-yl)-1,1-dimethyl-2-oxoethyl]-5-(3,5-dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrol-4-yl]propyl}(2-pyridin-4-ylethyl)amine;

2-(1,1-dimethyl-2-oxo-2-pyrrolidin-1-ylethyl)-5-(3,5-dimethylphenyl)-4-{2-[4-(pyridin-4-ylmethyl)piperazin-1-yl]ethyl}-6*H*-thieno[2,3-*b*]pyrrole;

2-(1,1-dimethyl-2-oxo-2-pyrrolidin-1-ylethyl)-5-(3,5-dimethylphenyl)-4-{2-[4-(pyridin-2-ylmethyl)piperazin-1-yl]ethyl}-6*H*-thieno[2,3-*b*]pyrrole;

2-(1,1-dimethyl-2-oxo-2-pyrrolidin-1-ylethyl)-5-(3,5-dimethylphenyl)-4-{2-[4-methylpiperazin-1-yl]ethyl}-6*H*-thieno[2,3-*b*]pyrrole;

2-(1,1-dimethyl-2-oxo-2-pyrrolidin-1-ylethyl)-5-(3,5-dimethylphenyl)-4-{2-[4-(pyridin-4-yl)piperazin-1-yl]ethyl}-6*H*-thieno[2,3-*b*]pyrrole;

2-[2-(2-azabicyclo[2.2.2]oct-2-yl)-1,1-dimethyl-2-oxoethyl]-5-(3,5-dimethylphenyl)-4-[2-(4-methylpiperazin-1-yl)ethyl]-6*H*-thieno[2,3-*b*]pyrrole;

4-[2-(4-allylpiperazin-1-yl)ethyl]-2-[2-(7-azabicyclo[2.2.1]hept-7-yl)-1,1-dimethyl-2-oxoethyl]-5-(3,5-dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrole;

2-[2-(7-azabicyclo[2.2.1]hept-7-yl)-1,1-dimethyl-2-oxoethyl]-5-(3,5-dimethylphenyl)-4-{2-[4-(2-morpholin-4-yl-2-oxoethyl)piperazin-1-yl]ethyl}-6*H*-thieno[2,3-*b*]pyrrole; and

2-[2-(7-azabicyclo[2.2.1]hept-7-yl)-1,1-dimethyl-2-oxoethyl]-5-(3,5-dimethylphenyl)-4-{2-[4-(pyridin-4-ylmethyl)piperazin-1-yl]ethyl}-6*H*-thieno[2,3-*b*]pyrrole;

or a salt, pro-drug or solvate thereof.

The compounds of Formula (I) may be administered in the form of a pro-drug which is broken down in the human or animal body to give a compound of the Formula (I). Examples of pro-drugs include in-vivo hydrolysable esters of a compound of the Formula (I).

Various forms of pro-drugs are known in the art. For examples of such pro-drug derivatives, see:

a) Design of Prodrugs, edited by H. Bundgaard, (Elsevier, 1985) and Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder, et al. (Academic Press, 1985);

b) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen and H. Bundgaard, Chapter 5 "Design and Application of Prodrugs", by H. Bundgaard p. 113-191 (1991);

c) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992);

d) H. Bundgaard, et al., Journal of Pharmaceutical Sciences, 77, 285 (1988); and

e) N. Kakeya, et al., Chem Pharm Bull, 32, 692 (1984).

An in-vivo hydrolysable ester of a compound of the Formula (I) containing a carboxy or a hydroxy group is, for example, a pharmaceutically-acceptable ester which is hydrolysed in the human or animal body to produce the parent acid or alcohol. Suitable pharmaceutically-acceptable esters for carboxy include C_{1-6}alkoxymethyl esters for example methoxymethyl, C_{1-6}alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, C_{3-8}cycloalkoxycarbonyloxyC_{1-6}alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters, for example 5-methyl-1,3-dioxolen-2-onylmethyl; and C_{1-6}alkoxycarbonyloxyethyl esters.

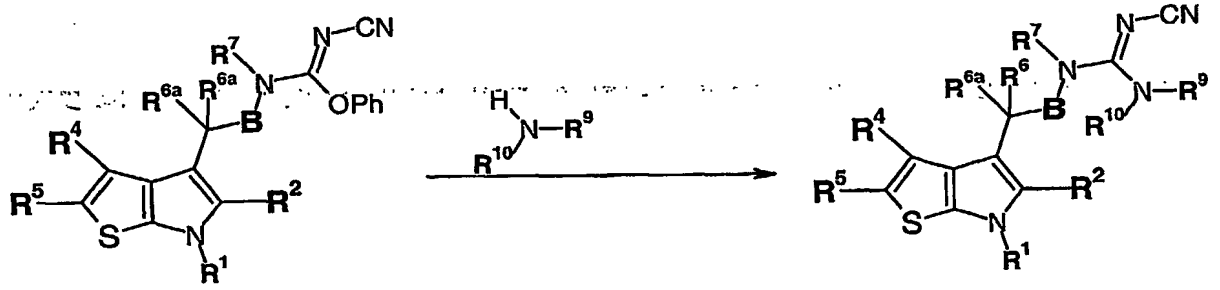
An in-vivo hydrolysable ester of a compound of the Formula (I) containing a hydroxy group includes inorganic esters such as phosphate esters (including phosphoramidic cyclic esters) and α-acyloxyalkyl ethers and related compounds which as a result of the in-vivo hydrolysis of the ester breakdown to give the parent hydroxy group/s. Examples of α-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxy-methoxy.

A selection of in-vivo hydrolysable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxycarbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and N-(dialkylaminoethyl)-N-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carboxyacetyl.

A suitable pharmaceutically-acceptable salt of a compound of the invention is, for example, an acid-addition salt of a compound of the invention which is sufficiently basic, for example, an acid-addition salt with, for example, an inorganic or organic acid, for example hydrochloric, hydrobromic, sulphuric, phosphoric, trifluoroacetic, citric or maleic acid. In addition a suitable pharmaceutically-acceptable salt of a compound of the invention which is sufficiently acidic is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a physiologically-acceptable cation, for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

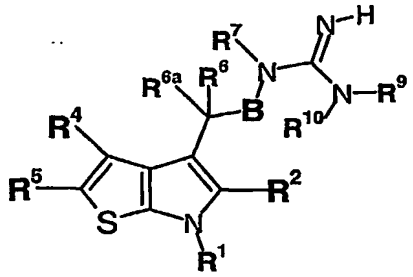
The compounds of Formula (I) can be prepared by a process comprising a step selected from (a) to (e) as follows, these processes are provided as a further feature of the invention:-

(a) Reaction of a compound of formula **XXXII** as follows



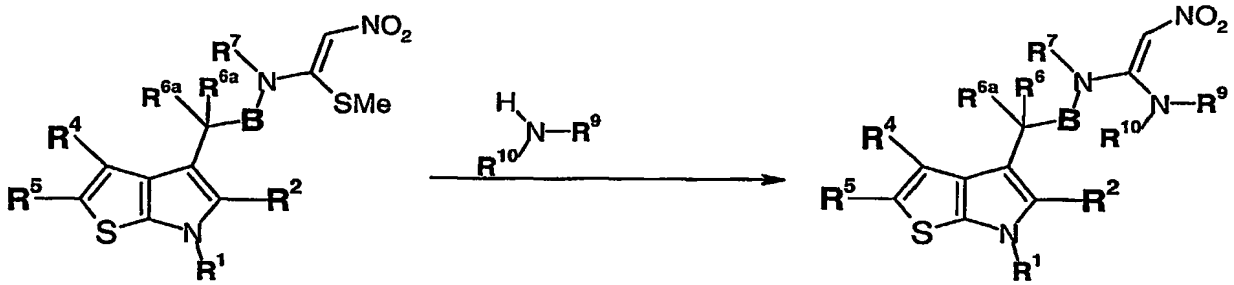
XXXII **XXXIII**

(b) Cleavage of the cyano group of compound of formula **XXXIII** in the presence of acid to produce compound of formula **XXXIV**



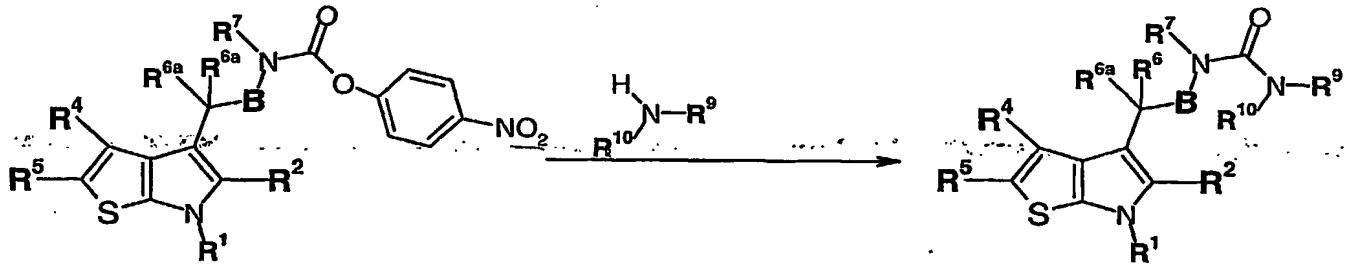
XXXIV

(c) Reaction of compound of formula **XXXV** as follows



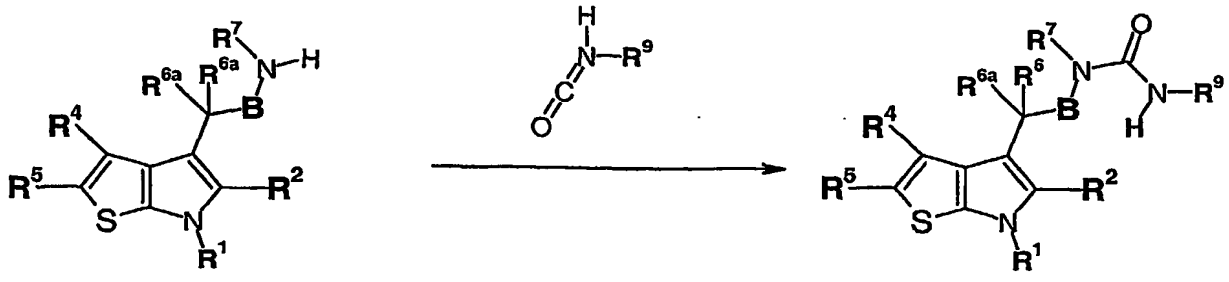
XXXV XXXVI

(d) Reaction of compound of formula **XXXVII** as follows



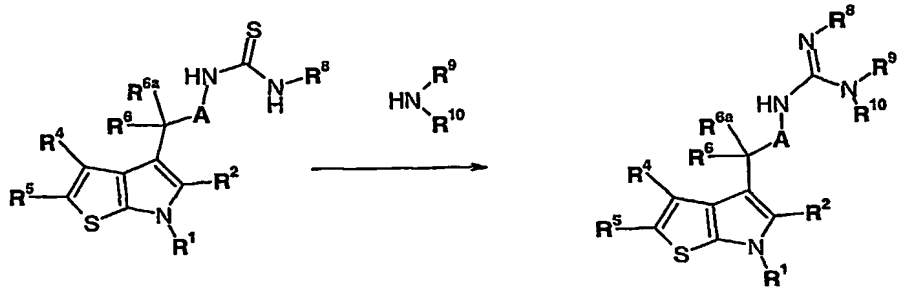
XXXVII XXXVIII

(e) Reaction of compound of formula **XXXIX** as follows



XXXIX XXXX

(f) to form a compound wherein **X** is nitrogen and Reaction of a compound of formula XXXXI as follows



XXXXI XXXXII

and thereafter if necessary:

i) converting a compound of the Formula (I) into another compound of the Formula (I);

ii) removing any protecting groups;

iii) forming a salt, pro-drug or solvate.

It will be appreciated by those skilled in the art that in the processes of the present invention certain functional groups such as hydroxyl or amino groups in the starting reagents or intermediate compounds may need to be protected by protecting groups. Thus, the preparation of the compounds of Formula (I) may involve, at an appropriate stage, the addition and subsequent removal of one or more protecting groups.

The protection and de-protection of functional groups is described in 'Protective Groups in Organic Chemistry', edited by J.W.F. McOmie, Plenum Press (1973) and 'Protective Groups in Organic Synthesis', 2nd edition, T.W. Greene and P.G.M. Wuts, Wiley-Interscience (1991).

A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *tert*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The de-protection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *tert*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with

a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

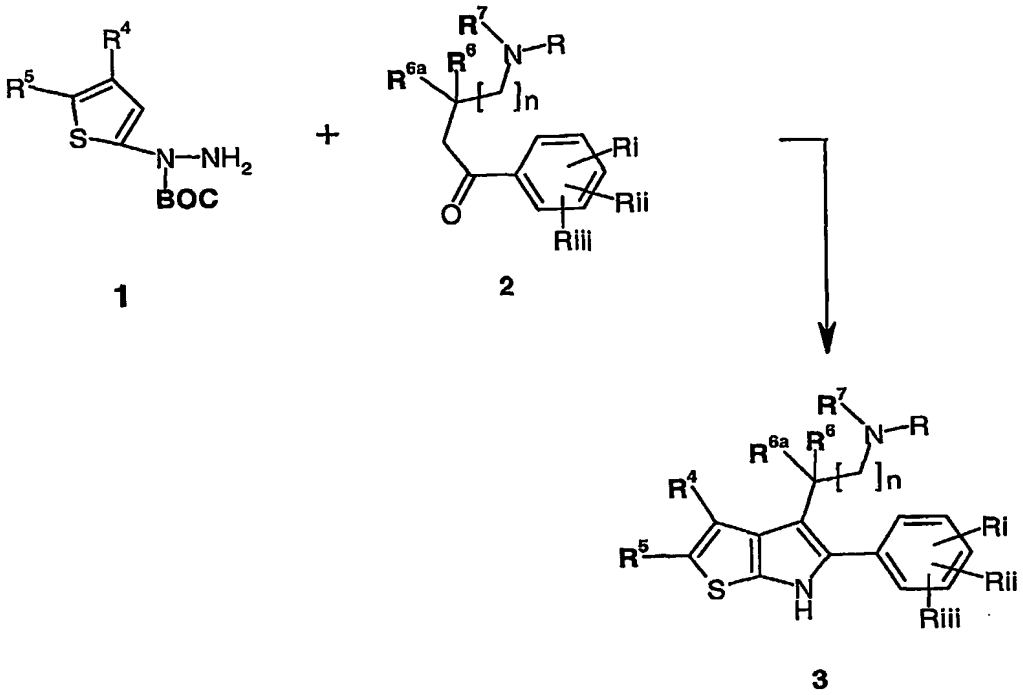
A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The de-protection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *tert*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

EXPERIMENTAL

GENERAL REACTION SCHEMES

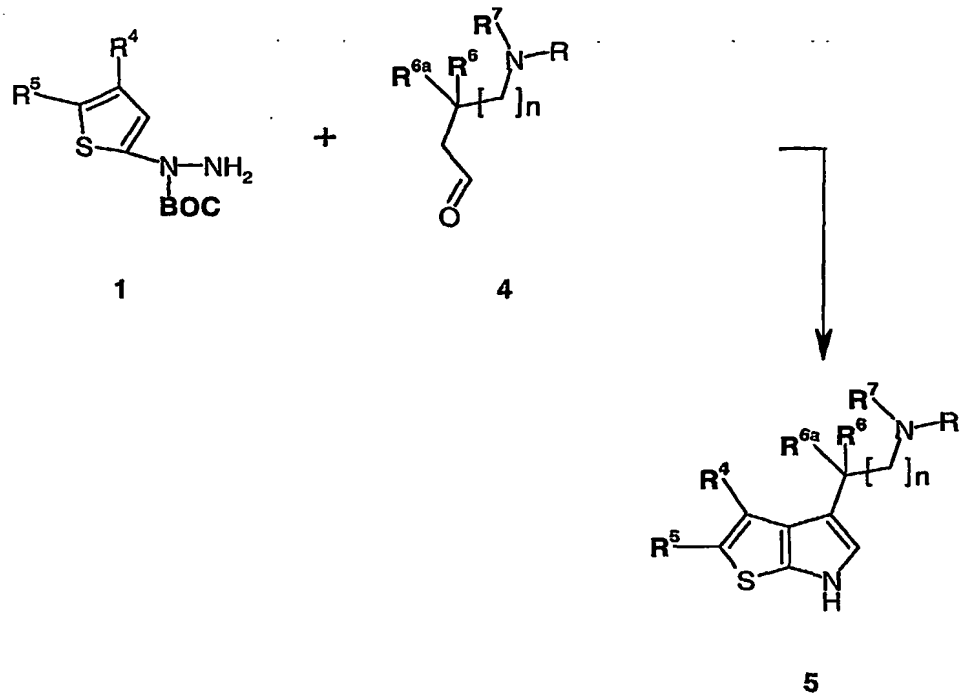
In the following schemes wherein Ri, Rii and Riii represent optional substituents on the phenyl ring which are optionally protected as necessary and R represents a protecting group, group **C** has been depicted as substituted phenyl for illustration purposes only. Other definitions of **C** are also appropriate.



1 2 3

Scheme a

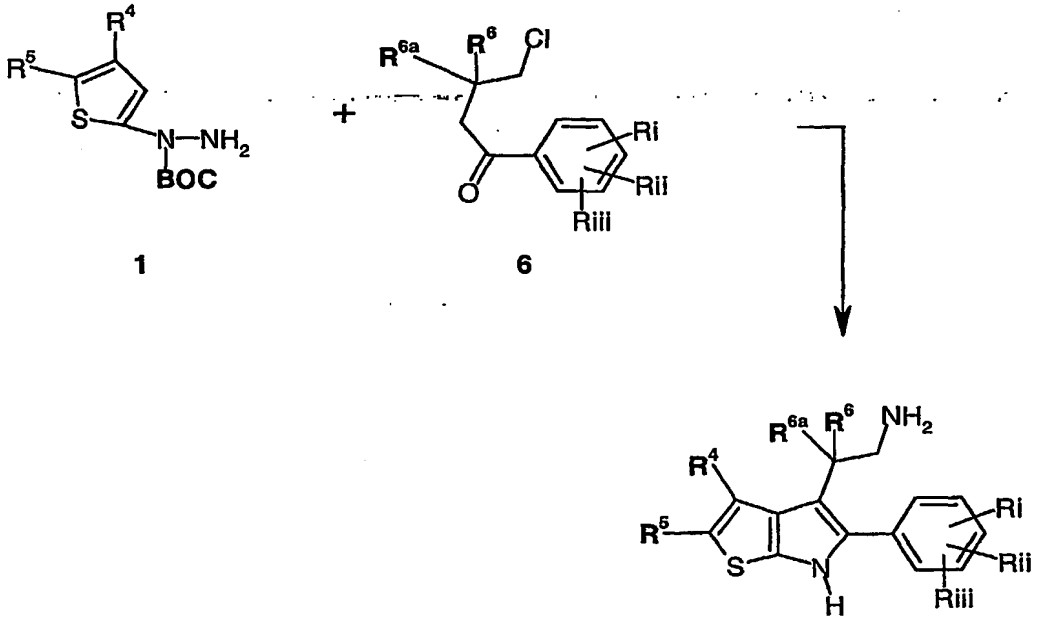
Thienopyrroles, such as **3** can be synthesised by the classic Fisher thienopyrrole synthesis reaction by the condensation of a hydrazine-HCl **1** and a ketone **2**, bearing hydrogen atoms α to the carbonyl (Scheme a). Treatment of these reactants in a suitable solvent, such as acetic acid, ethanol, *sec*-butanol, toluene, in the presence of an acid, such as sulphuric, hydrochloric, polyphosphoric and/or a Lewis acid, for example, boron trifluoride, zinc chloride, magnesium bromide, at elevated temperatures (for example 100 °C), gives the desired product. R represents a protecting group, eg *tert*-butylcarbamate or phthalimide.



1 4 5

Scheme b

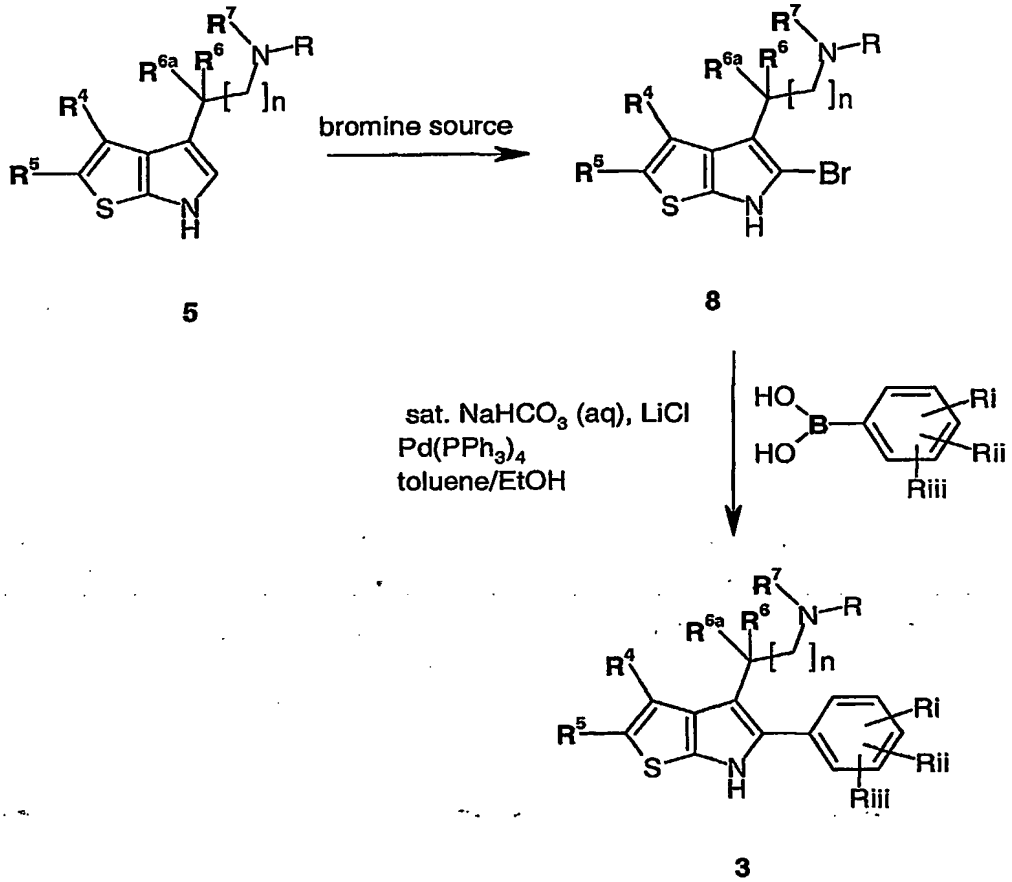
Thienopyrroles, such as represented in structure **5**, can also be made using aldehydes **4**, bearing hydrogen atoms α to the carbonyl, by cyclization using the conditions above. In this case the substituent at the 2-position must be added later (see scheme d).



1 6 7

Scheme c

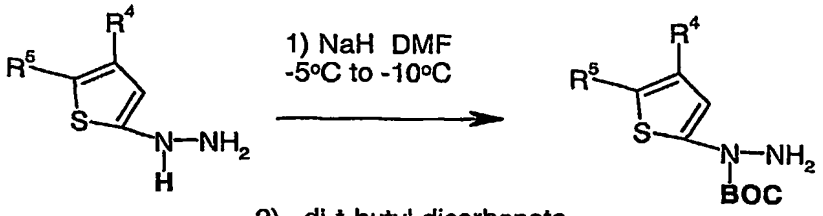
Thienopyrrole may also be synthesised utilising the Granburg reaction, wherein a hydrazine **1** is mixed with ketone **6**, bearing a chlorine atom γ to the carbonyl, and heated in a suitable solvent such as ethanol, *sec*-butanol, toluene at a temperature between 50 °C and 120 °C (Scheme c).



5 **8** **3**

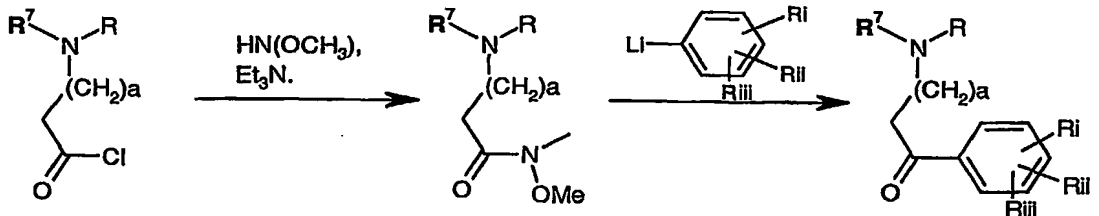
Scheme d

The thienopyrrole **5** can be treated with a 'bromine source', such as molecular bromide, pyridinium tribromide, pyrrolidone hydrobromide or polymer supported reagent equivalents, in an inert solvent such as chloroform, methylene chloride at -10 °C to 25 °C to yield the 2-bromo compound **8** (Scheme d). Reaction under Suzuki conditions with a palladium(0) catalyst, a weak base such aqueous sodium carbonate or saturated sodium hydrogen carbonate and the like, and a substituted aryl boronic acid from commercial sources or prepared (as described in: Gronowitz, S.; Hornfeldt, A.-B.; Yang, Y.,-H *Chem. Sci.* **1986**, *26*, 311-314), in an inert solvent such as toluene, benzene, dioxane, THF, DMF and the like, with heating between 25 °C and 100 °C, preferably 80 °C, for a period of 1-12 hours, to give the desired compound **3**.



3. 1

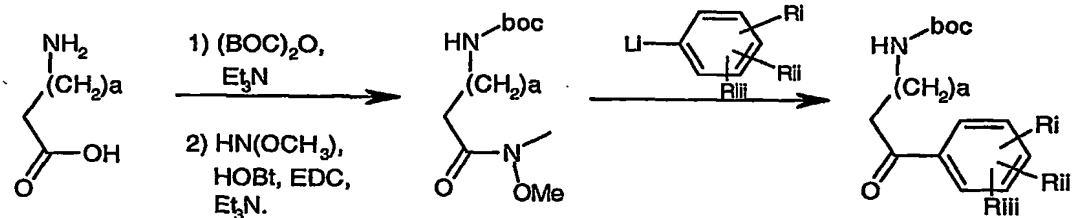
The thiophene **1** can be synthesised by reaction of a hydrazine under the preferred conditions of sodium hydride in DMF at a temperature between -10 °C and -5 °C, followed by reaction with di-tert-butyldicarbonate in THF under reflux.



9 10 2

Scheme e.

Substituted ketones **2** can be prepared, as outlined in Scheme e starting from appropriate acid chlorides such as **9**. Treatment of the acid chloride with *N,N*-dimethylhydroxylamine hydrochloride in the presence of an amine base such as triethylamine, and a suitable solvent such as methylene chloride at a temperature of -10 °C to 25 °C, yields the amide **10**. Further reaction with a substituted aryl organolithium (prepared essentially as described in Wakefield B, J.; *Organolithium Methods* Academic Press Limited, **1988**, pp. 27-29 and references therein) in an inert solvent such as tetrahydrofuran, diethyl ether, benzene, toluene or mixture thereof and the like, at a temperature between -100 °C and 0 °C then quenching of the reaction mixture with a mineral acid such as hydrochloric acid, yields the aryl ketone **2**.



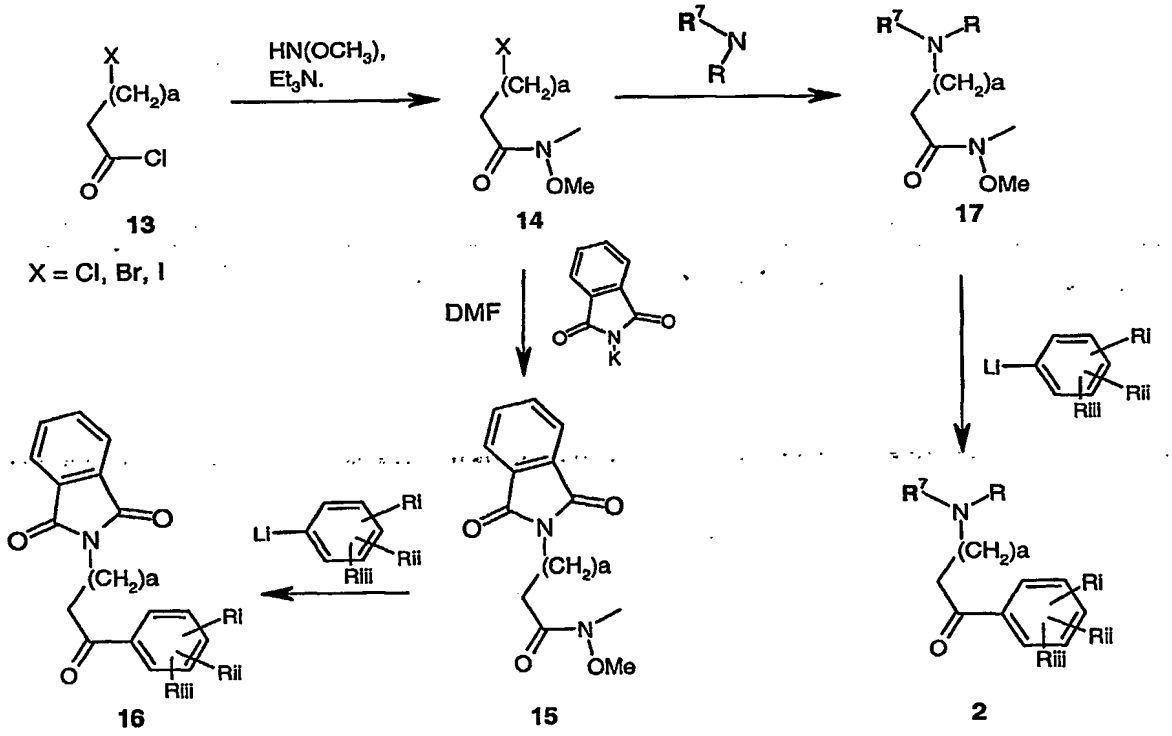
11 12 2

Scheme f.

Commencing with a readily available amino acid with a suitable chain length [a] **11**, the nitrogen atom can be brought in at the beginning of the synthesis by the route shown in

Scheme f. Protection of the amine group of **11** with a *tert*-butylcarbamate group is achieved by condensation with di-*tert*-butyl di-carbonate in the presence of an amine base, for example triethylamine, in an inert solvent such as methylene chloride, chloroform, benzene, toluene, tetrahydrofuran and mixtures thereof and the like, at a temperature of -10 °C to 25 °C.

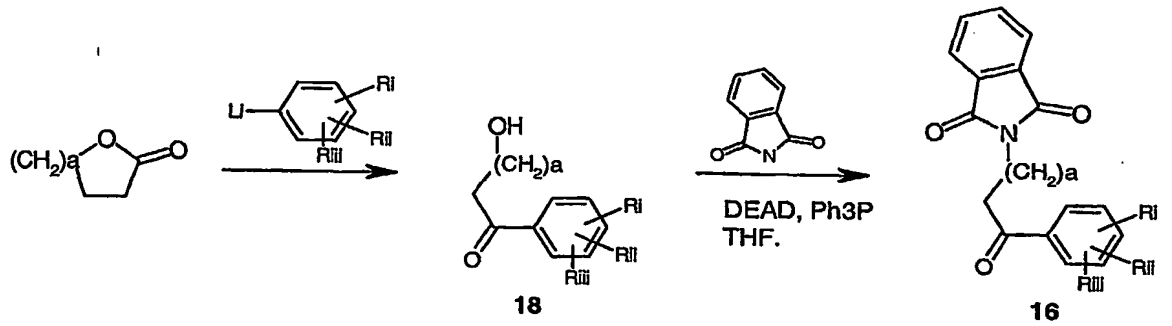
Coupling of the acid product with *N,N*-dimethylhydroxylamine in the presence of a coupling reagent 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) or 1,3-dicyclohexylcarbodiimide (DCC) or the like, with or without 1-hydroxybenotriazole (HOBt), and suitable amine base, such as triethylamine and the like, in an inert solvent such as methylene chloride, chloroform, dimethylformamide, or mixture thereof, at or near room temperature for a period of 3 to 24 hours provided the corresponding coupled product **12**. Following the same route described above for scheme d, the aryl group can then be installed.



Scheme g.

Scheme g illustrates another method for the synthesis of ketone such as **2** and **16**, where the nitrogen group is introduced at a latter stage. As above a Weinreb amide **14** can be synthesised from an acid chloride. Treatment with the required amine, in an inert solvent such as THF, toluene, water and the such like can displace the group X to give **17**. As above the aryl group can be introduced by displacement of the Weinreb amide with a suitable aryl lithium nucleophile. Alternatively the nitrogen atom can be introduced already protected as a phthalimide by displacement of the group x by potassium phthalimide, or similar salt thereof,

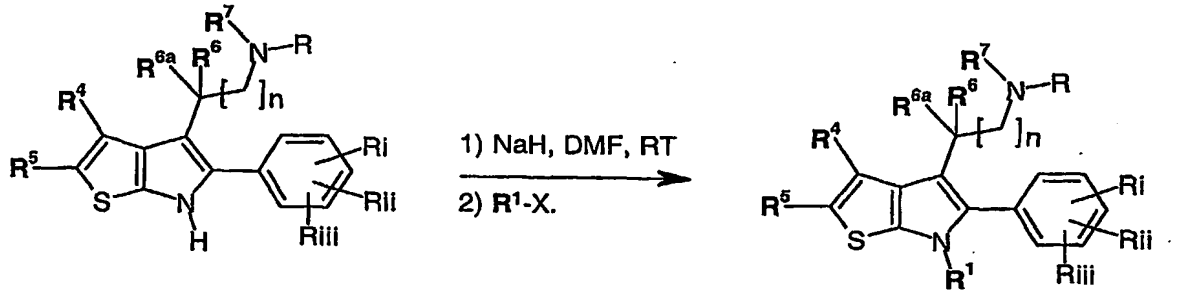
by heating in an inert polar solvent such as DMF, DMSO, THF, toluene with or without the presence of a catalyst such as tetrabutylammonium iodide and the such like, to yield the compound **15**. Again displacement of the Weinreb amide with an organolithium species completes the synthesis of a ketone suitable for cyclization under the Fischer condition described above for thienopyrrole synthesis.



18 **16**

Scheme h.

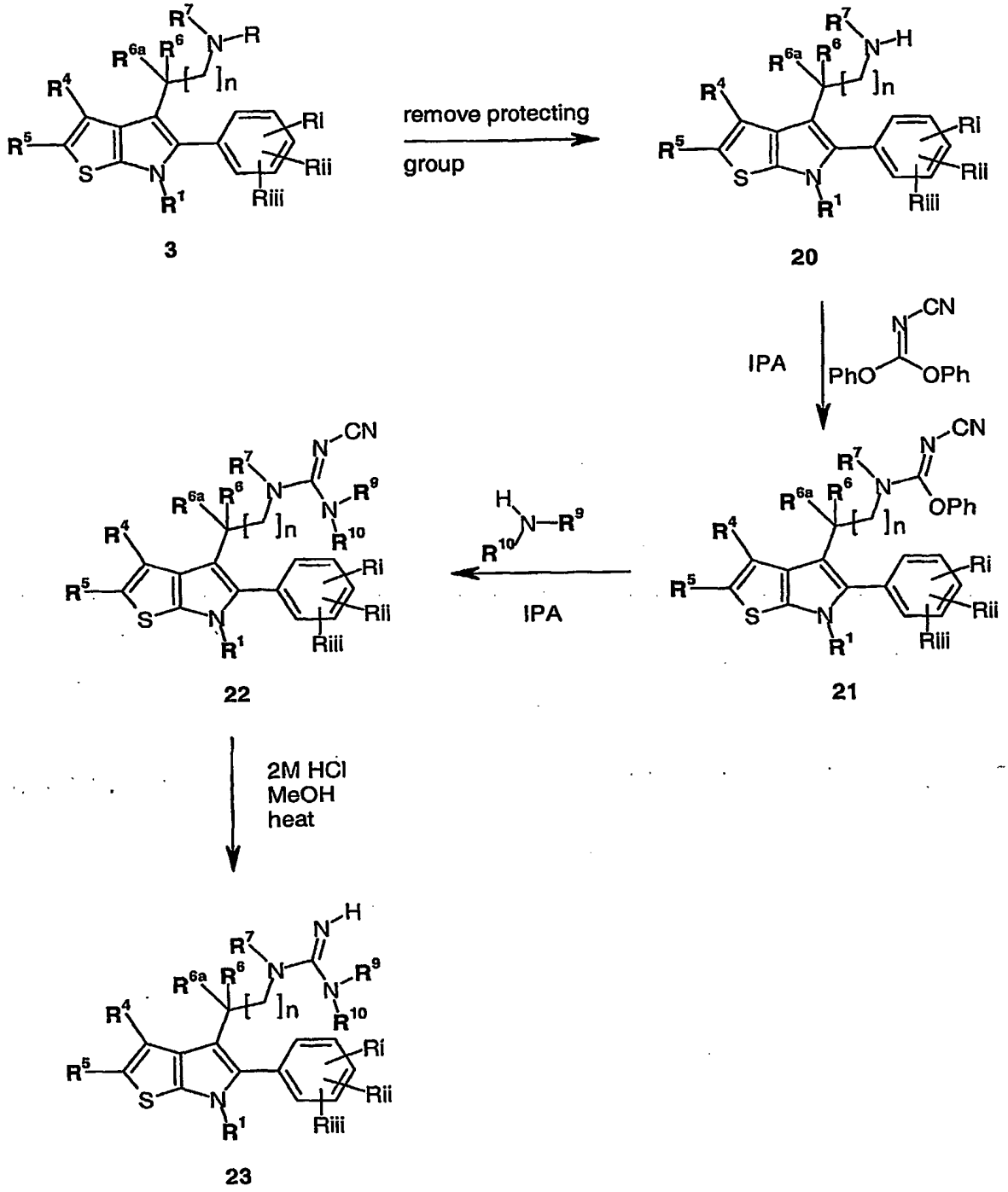
An alternative approach to a phthalimide protected nitrogen ketone, such as **16**, can be taken by firstly treating a lactone, with an organolithium species as in the above schemes in a suitable solvent such as THF or ether at a low temperature of between –100 °C and –50 °C to yield a primary alcohol **18** (Scheme h). The hydroxyl function of **18** is replaced with a phthalimide group by a Mitsunobu reaction with an activating agent such as diethyldiazocarboxylate (DEAD), diisopropyldiazocarboxylate or the like with triphenylphosphine, tri-butylphosphine and the like, in an inert solvent such as benzene, toluene, tetrahydrofuran or mixtures thereof to give the desired ketone **16**.



19 **3**

If the group R^1 was not present on the starting hydrazine before cyclization to form an thienopyrrole it may be added post cyclization by an alkylation reaction (**19**→**3**). The thienopyrrole is de-protonated by a strong base, such as sodium hydride, *n*-butyl lithium, lithium diisopropylamine, sodium hydroxide, potassium *tert*-butoxide in a suitable inert

solvent such as THF, DMF, DMSO and the such like, and an alkyl halide added and the mixture stirred at room temperature.

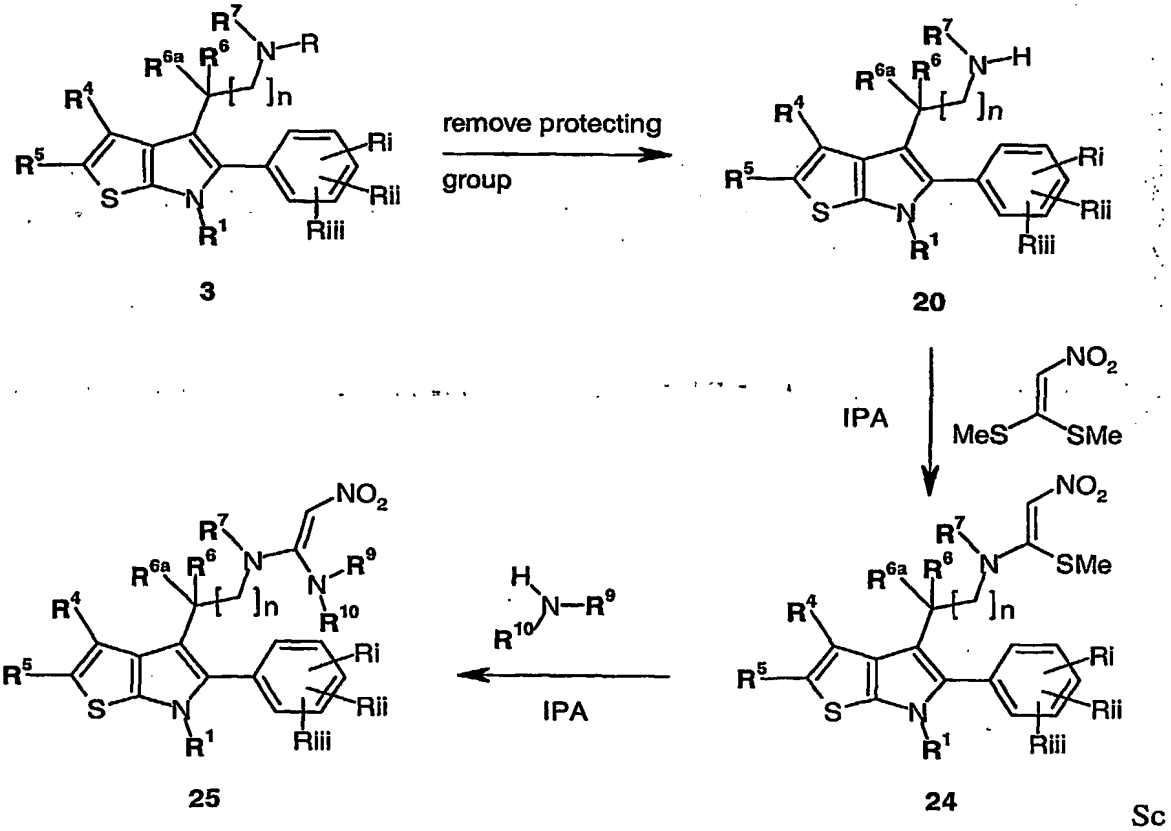


3 20 21 22 23

Scheme i

Depending on the route used above a thienopyrrole **20** suitable for conversion to a cyano-guandine can be formed by removal of the protecting group, for example if a *tert*-butylcarbamate group was used then removal is accomplished using a strong acid, for

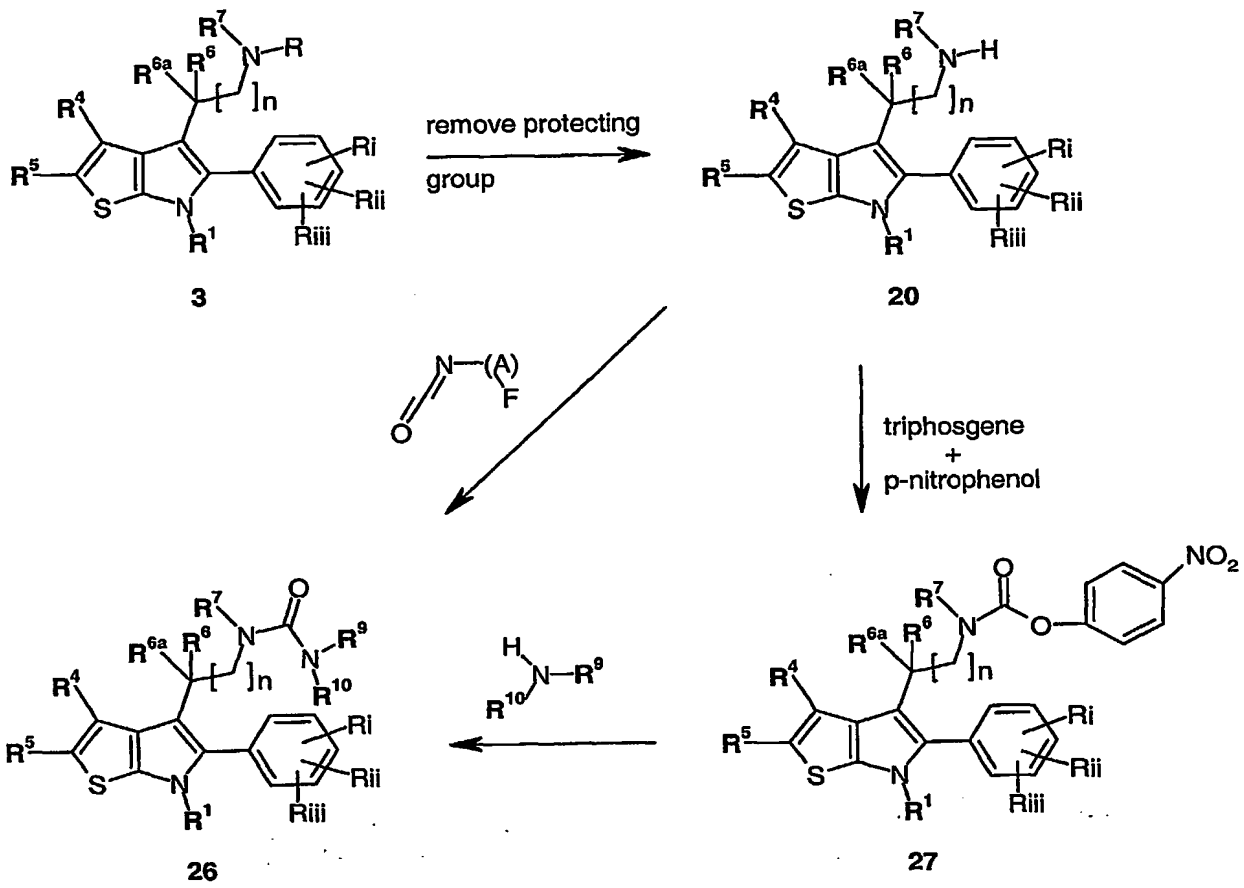
example trifluoroacetic acid or hydrochloric acid in an inert solvent such as methylene chloride, chloroform, THF or dioxane at a temperature between –20 °C and 25 °C. A phthalimide group, for example, can be removed by hydrazine in a suitable solvent for example methanol, ethanol, methylene chloride, chloroform, THF dioxane at a temperature between –20 °C and 25 °C. The primary amine **20** can be converted to a cyano-guanidine **22** by the two step process of reaction with diphenyl cyanocarbonimidate in an inert organic solvent such as *iso*-propyl alcohol, methylene chloride, chloroform, benzene, tetrahydrofuran and the like, at a temperature between –20 °C and 50 °C, followed by condensation with an appropriately substituted amine in an inert organic from the list above, with heating at a temperature between –20 °C and 100 °C (Scheme I **20**→**21**→**22**). Further treatment of **22** with 2 molar Hydrochloric acid in methanol at elevated temperature yields guanidine compounds **23**.



3 **20** **24** **25**

Scheme j.

Similarly, reaction with 1,1'-bis(methylthio)-2-nitroethylene in an inert solvent such methylene chloride, chloroform, benzene, tetrahydrofuran and the like, followed by condensation with an appropriately substituted amine in an inert organic solvent from the list above yields the nitroethyleneimidazo[1,2-*a*]pyridine **25** (Scheme j, **20**→**24**→**25**).



Scheme k.

Again in a similar fashion the suitable thienopyrrole **20**, derived from de-protection, can be converted to a urea by either direct treatment with an iso-cyanate in an inert solvent such as methylene chloride, chloroform or THF and the such like, or by a two step procedure of reaction with triphosgene (**20**→**27**) followed by addition of an amine (**27**→**26**), bearing the required substitution to yield **26**.

EXAMPLES

The invention will now be illustrated with the following non-limiting Examples in which, unless otherwise stated:

(i) evaporations were carried out by rotary evaporation in *vacuo* and work-up procedures were carried out after removal of residual solids such as drying agents by filtration;

(ii) operations were carried out at room temperature, that is in the range 18-25°C and under an atmosphere of an inert gas such as argon or nitrogen;

(iii) yields are given for illustration only and are not necessarily the maximum attainable;

(iv) the structures of the end-products of the Formula (I) were confirmed by nuclear (generally proton) magnetic resonance (NMR) and mass spectral techniques; proton magnetic resonance chemical shift values were measured on the delta scale and peak multiplicities are shown as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad; q, quartet, quin, quintet;

(v) intermediates were not generally fully characterised and purity was assessed by thin layer chromatography (TLC), high-performance liquid chromatography (HPLC), infra-red (IR) or NMR analysis;

(vi) chromatography was performed on silica (Merck Keiselgel: Art.9385);

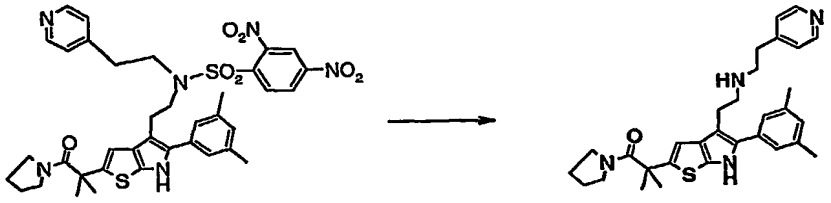
(vii) isolute™ refers to silica (SiO_2) based columns with irregular particles with an average size of 50μm with nominal 60 Å porosity [Source: Jones Chromatography, Ltd., Glamorgan, Wales, United Kingdom].

Abbreviations

DCC	1,3-dicyclohexylcarbodiimide
DEAD	diethylazodicarboxylate
DMSO	dimethyl sulphoxide
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
HOBt	1-hydroxybenzotriazole
THF	tetrahydrofuran

Example 1

2-[2-(1,1-dimethyl-2-oxo-2-pyrrolidin-1-ylethyl)-4-*N*-(2-pyridin-4-ylethyl)aminoethyl-5-(3,5-dimethylphenyl)--6*H*-thieno[2,3-*b*]pyrrole



14 **Example 1**

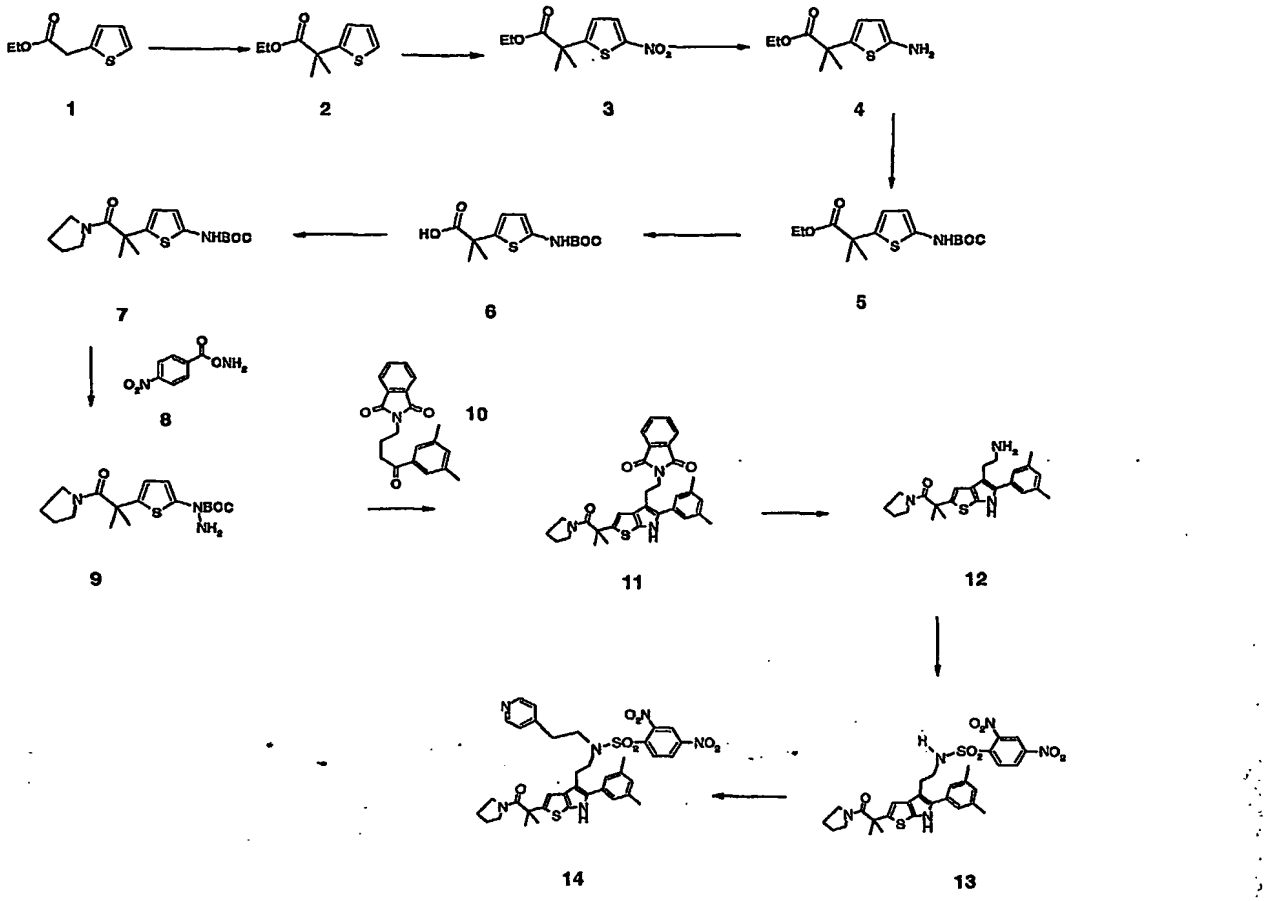
A solution of **14** (0.486 g; 0.649 mmol) in CH_2Cl_2 (6 ml) was treated with n-propylamine (0.5 ml). The mixture was stirred at ambient temperature for 1 hour. After evaporation to dryness, the residue was taken up in AcOEt and treated at 0°C with an HCl / ether to give a precipitate which was washed with AcOEt and ether.

Yield: 81 %

^{1}H NMR (DMSOd6): 1.55 (s, 6H); 1.64 (m, 4H); 2.33 (s, 6H); 3-3.5 (m, 12H); 9.89 (s, 1H); 6.95 (s, 1H); 7.08 (s, 2H); 7.6-7.9 (br m, 1H); 8.04 (d, 2H); 8.93 (d, 2H).

MS-ESI: 515 $[M+H]^+$

The starting material was prepared as follows:



To a suspension of NaH (54 g; 1.35 mol), and 18-crown-6 in THF (2 l) stirred at ambient temperature under argon atmosphere, **1** (100 g; 0.588 mol) was added over a period of 30 minutes. After stirring overnight, the mixture was cooled at 0°C and methyl iodide was added dropwise. The mixture was stirred at 18°C for 3 hours, poured into a saturated solution of NH_4Cl and extracted with AcOEt. The organic phase was evaporated and purified by flash chromatography eluting with petroleum ether / ethyl acetate 95/5 to give **2** as an oil.

Yield: 90 %

^1H NMR ($CDCl_3$): 1.20 (t, 3H); 1.63 (s, 6H) ; 4.10 (q, 2H) ; 6.92 (m, 2H) ; 7.17 (m, 1H).

Nitronium tetrafluoroborate (77.9 g; 0.586 mol) was added at –55°C to a solution of **2** (105.6 g; 0.583 mol) in DME (1.5 l). The mixture was allowed to warm up at –10°C over 4 hours. After extraction with ethyl acetate, the organic phase was purified by flash chromatography, eluting with petroleum ether / AcOEt 95/5 to give **3**.

Yield: 86 %

^{1}H NMR ($CDCl_3$): 1.23 (t, 3H); 1.65 (s, 6H); 4.14 (q, 2H); 6.90 (d, 1H); 7.75 (d, 1H).

A suspension of **3** (101.7 g; 0.41 mol) and 10 % Pd/C (15 g) in a mixture of ethanol (700 ml) and ethyl acetate (300 ml) was hydrogenated under hydrogen atmosphere (5 bars) for 5 hours. After filtration of the catalyst on celite, the residue was evaporated and redissolved in THF (900 ml); di-tert-butyl dicarbonate (100 g; 0.46 mol) was added and the mixture was refluxed for 16 hours. After evaporation of the solvents, the resulting solid was taken up in petroleum ether and filtered to give **5**.
Yield: 68 %
^{1}H NMR ($CDCl_3$): 1.20 (t, 3H); 1.48 (s, 9H); 1.58 (s, 6H); 4.10 (q, 2H); 6.30 (m, 1H); 6.60 (m, 1H).

A solution of **5** (50 g; 0.16 mol) and 2N NaOH (160 ml) in ethanol (300 ml) was refluxed for 1 h 30. After evaporation to dryness, the residue was partitioned between water and ether. The aqueous layer was acidified with saturated citric acid and extraction with ethyl acetate to give after evaporation a solid, which was triturated in pentane and filtered to give **6** as a solid.
Yield: 100%
^{1}H NMR ($DMSOd_6$): 1.48 (m, 15H); 6.30 (d, 1H); 6.59 (d, 1H).

A solution of **6** (20.1 g; 0.07 mol), EDCI (20.1 g; 0.105 mol) and DMAP (2.56 g; 0.021 mol) in dichloromethane (200 ml) was stirred under argon atmosphere for 10 minutes. Pyrrolidine (11.69 ml; 0.14 mol) was then added and the mixture was stirred overnight at ambient temperature. After evaporation to dryness, the residue was purified by flash chromatography eluting with AcOEt / petroleum ether 40/60 to give after trituration in ether / pentane **7** as a solid.
^{1}H NMR ($CDCl_3$): 1.51 and 1.57 (s, 15 H); 1.7 (m, 4H); 3.03 (br, 2H); 3.50 (br, 2H); 6.35 (d, 1H); 6.48 (d, 1H); 7.26 (br, 1H).

7 (17 g; 0.05 mol) was added under argon atmosphere to a suspension of NaH 60 % (2.42 g; 0.06 mol) in dioxan (240 ml). The mixture was stirred at 100°C for 3 hours. After cooling to 10°C, **8** (10.1 g; 0.055 mol) was added. The reaction mixture was stirred at ambient temperature overnight. After filtration of the insoluble, the filtrate was evaporated and

purified by flash chromatography, eluting with AcOEt / petroleum ether 45/55 to give **9** as a white solid.

Yield: 89.5 %

^{1}H NMR ($CDCl_3$): 1.55 and 1.57 (s, 15 H); 1.71 (s, 4H); 3.04 (s, 2H); 3.50 (s, 2H); 6.53 (d, 2H); 6.70 (s, 2H).

A solution of **9** hydrochloride salt (4 g; 0.0102 mol) and **10** (6.6 g; 0.0205 mol) in AcOH (20 ml) was heated at 120°C under argon atmosphere for 3 hours. The reaction mixture was diluted with saturated NH_4Cl and extracted with AcOEt. After evaporation, the crude was purified by flash chromatography eluting with AcOEt / petroleum ether 50/50 to give **11** as a foam.

Yield: 53 %

MS-ESI : 540 $[M+H]^+$

^{1}H NMR ($CDCl_3$): 1.53 and 1.58 (s, 6H); 1.69 (s, 4H); 2.29 (s, 6H); 3.12 (m, 4H); 3.52 (s, 2H); 3.91 (m, 2H); 6.80 (m, 2H); 7.02 (s, 2H); 7.6-7.8 (m, 4H); 8.10 (s, 1H).

A solution of **11** (0.534 g; 0.99 mmol) and hydrazine (1 ml) in a mixture of EtOH (2 ml) and CH_2Cl_2 (2 ml) was stirred under argon atmosphere at ambient temperature overnight. After evaporation, the crude was extracted in a mixture of CH_2Cl_2 and saturated $NaHCO_3$. The organic layer was evaporated to give **12** as a foam.

Yield: 90 %

^{1}H NMR ($CDCl_3$): 1.52 and 1.62 (s, 6H); 1.69 (s, 4H); 2.33 (s, 6H); 2.80-3.2 (m, 6H); 3.52 (m, 2H); 6.74 (s, 1H); 6.93 (s, 1H); 7.05 (s, 2H); 8.15 (s, 1H).

MS-ESI: 410 $[M+H]^+$

2,4 dinitrobenzylsulfonyl chloride (0.238 g; 0.892 mmol) was added at 0°C, under argon atmosphere to a solution of **12** (0.365 g; 0.892 mmol) and collidine (0.118 ml; 0.892 mmol) in CH_2Cl_2 (5 ml). The mixture was stirred at 20°C for 1 hour. After evaporation, the crude was purified by flash chromatography eluting with CH_2Cl_2 / EtOH 96/4 to give **13**.

Yield: 90 %

MS-ESI: 640 $[M+H]^+$

DEAD (0.295 ml; 1.5 mmol) was added at 0°C under argon atmosphere to a solution of **13** (0.48 g; 0.75 mmol), PPh_3 (0.393 g; 1.5 mmol) and 2-hydroxyethyl-4-pyridine (0.185 g; 1.5 mmol) in THF (12 ml). The mixture was stirred at ambient temperature for 2 hours and purified by flash chromatography eluting with AcOEt / petroleum ether 80/20 to give **14**.

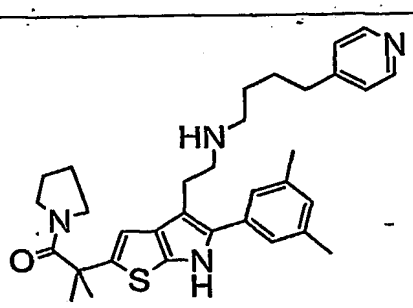
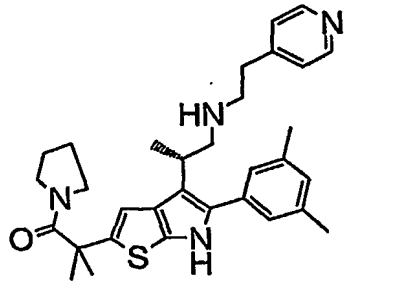
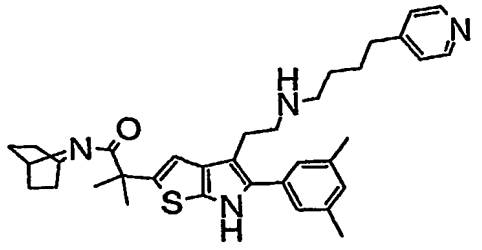
Yield: 86 %

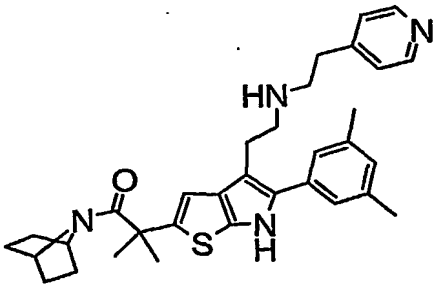
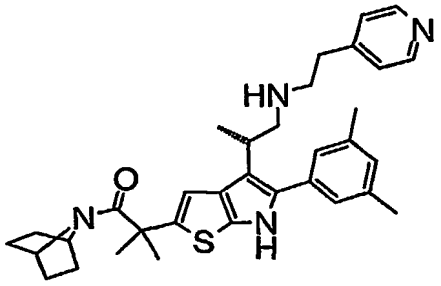
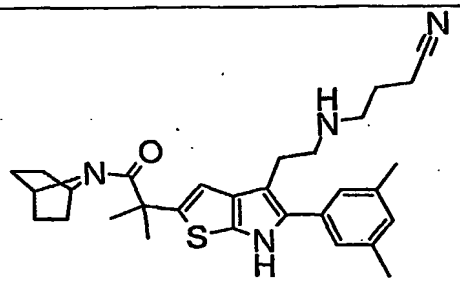
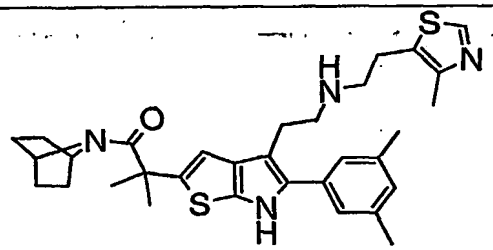
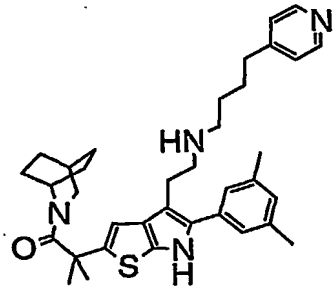
^1H NMR ($CDCl_3$) : 1.55 (s, 6H) ; 1.55-1.8 (m, 4H) ; 2.3 (s, 6H) ; 2.75 (t, 2H) ; 3-3.2 (m, 4H) ; 3.4-3.7 (m, 6H) ; 6.71 (s, 1H) ; 6.88 (d, 2H) ; 6.93 (s, 1H) ; 6.94 (s, 2H) ; 7.86 (d, 1H) ; 8.20-8.25 (m, 2H) ; 8.31 (s, 1H) ; 8.43 (d, 2H).

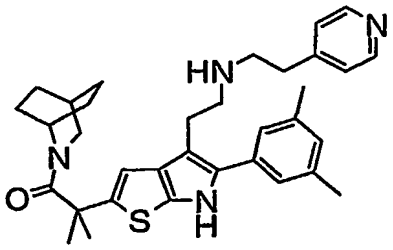
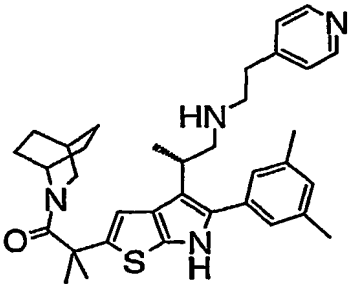
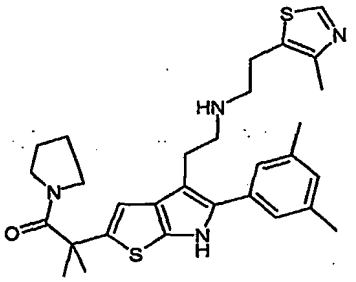
Examples 1.11 – 1.11

Following a procedure similar to that described in Example 1, the compounds of Table1 were prepared and purified by flash chromatography eluting with a gradient of 0-5% 3.5N NH_3-MeOH / CH_2Cl_2

Table1

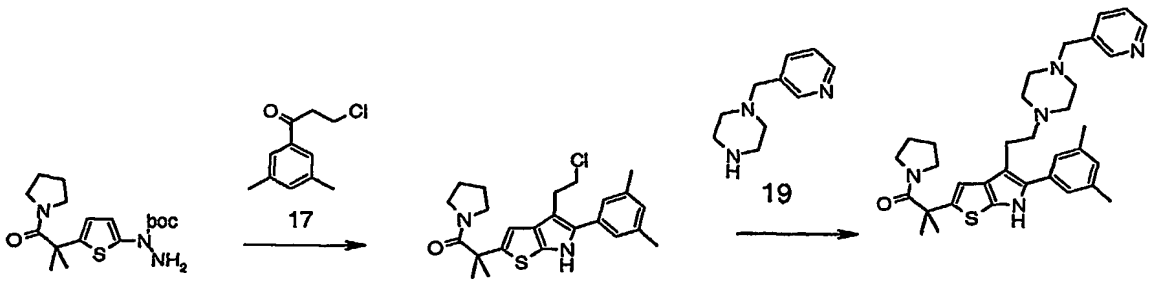
Example		MS-ESI
1.1		543 $[M+H]^+$
1.2		529 $[M+H]^+$
1.3		569 $[M+H]^+$

Example		MS-ESI
1.4		541 $[M+H]^+$
1.5		555 $[M+H]^+$
1.6		503 $[M+H]^+$
1.7		561 $[M+H]^+$
1.8		583 $[M+H]^+$

Example		MS-ESI
1.9		555 $[M+H]^+$
1.10		569 $[M+H]^+$
1.11		534 $[M+H]^+$

Example 2

2-[2-(1,1-dimethyl-2-oxo-2-pyrrolidin-1-ylethyl)-4-{2-[1-(pyridin-3-ylmethyl)piperazin-4-yl]ethyl}-5-(3,5-dimethylphenyl)--6*H*-thieno[2,3-*b*]pyrrole



9 18 Example 2

A mixture of **18** (0.362 g; 0.844 mmol), **19** (0.3 g; 1.68 mmol), K_2CO_3 (0.233 g; 1.68 mmol) in acetonitrile (6 ml) was heated at 85°C under argon atmosphere for 5 hours. The mixture was extracted with AcOEt and the organic layer was evaporated and purified by flash chromatography, eluting with CH_2Cl_2 3.5N NH_3 in MeOH 95/5 to give after trituration with ether-pentane **Example 2** as a solid.

Yield: 62 %

MS-ESI: 570 $[M+H]^+$

^1H NMR ($CDCl_3$) : 1.64 (s, 6H) ; 1.6-1.7 (m br, 4H) ; 2.34 (s, 6H) ; 2.4-2.8 (m, 10H) ; 2.9-3 (m, 2H) ; 3.1-3.2 (m, 2H) ; 3.45-3.65 (m, 4H) ; 6.74 (s, 1H) ; 6.94 (s, 1H) ; 7.05 (s, 2H) ; 7.67 (d, 2H) ; 8.2 (s, 1H) ; 8.5 (d, 2H).

The starting material was prepared as follows:

A solution of **9** hydrochloride salt (2 g; 0.005 mol), **17** (2.16 g; 0.01 mol) in sec-butanol (5 ml) was heated at 105°C under argon atmosphere for 2 hours and at 60°C overnight. The solvent was evaporated and the residue purified by flash chromatography eluting with petroleum ether / AcOEt 60/40 to give **18.**

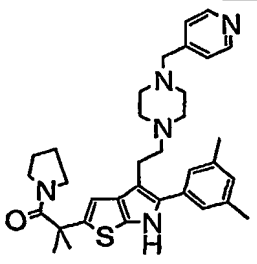
MS-ESI: 429 $[M+H]^+$

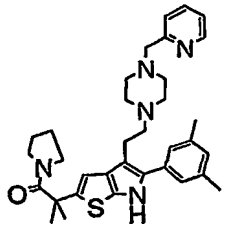
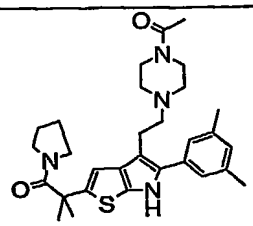
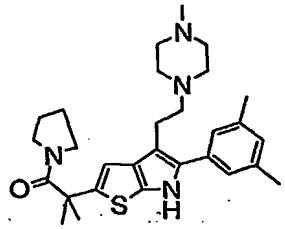
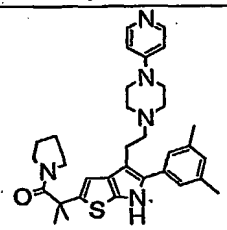
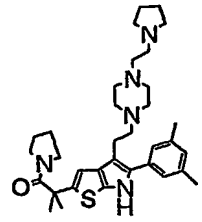
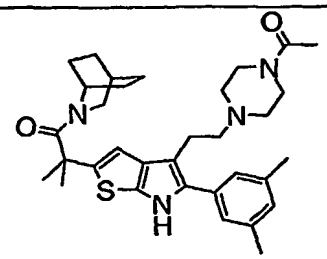
^1H NMR (DMSO d6) : 1.53 (s, 6H) ; 1.64 (m br, 4H) ; 2-2.15 (m, 1H) ; 2.3 (s, 6H) ; 2.4-2.5 (m br, 1H) ; 3-3.10 (m, 4H) ; 3.35-3.5 (m, 7H) ; 3.8 (m br, 2H) ; 6.83 (s, 1H) ; 6.91 (s, 1H) ; 7.09 (s, 2H).

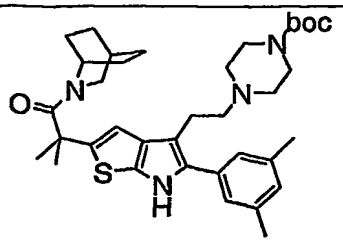
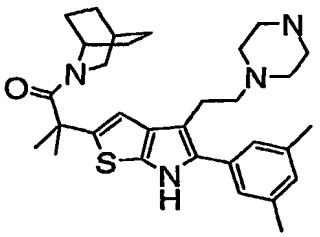
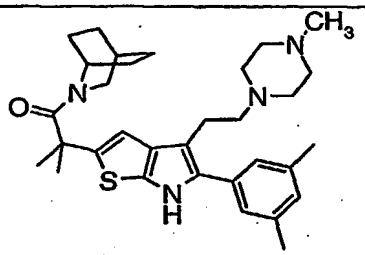
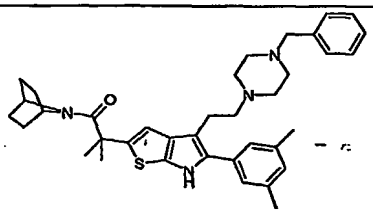
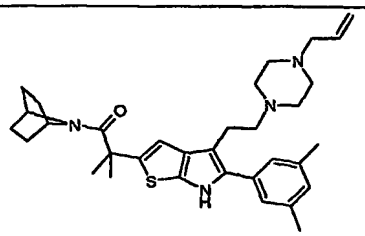
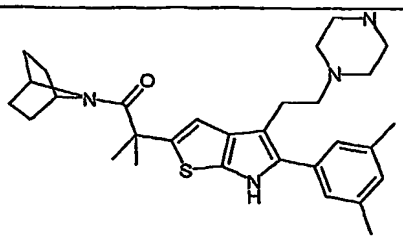
Examples 2.1 – 2.33

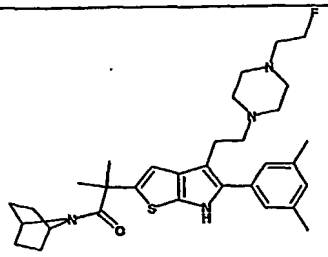
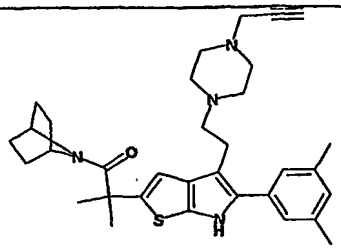
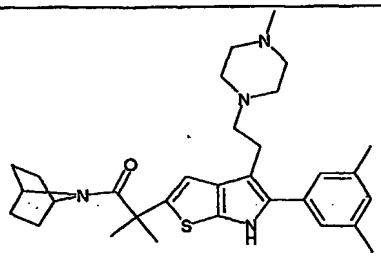
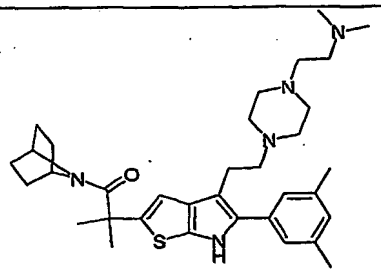
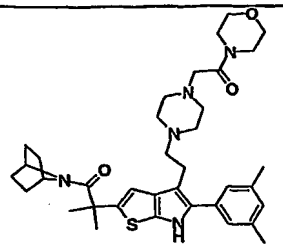
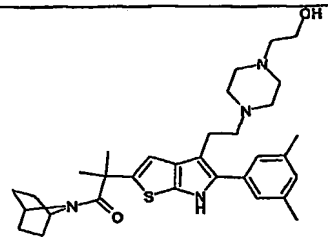
Following a procedure similar to that described in example 4, the compounds of table 3 were prepared.

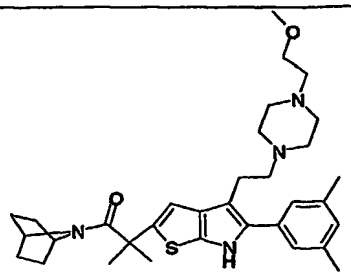
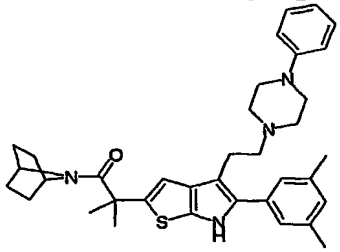
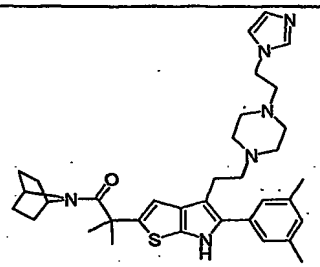
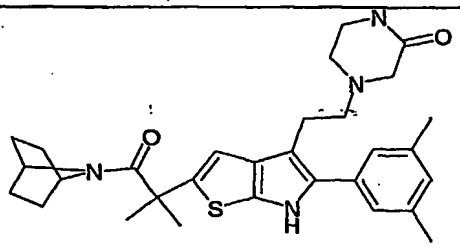
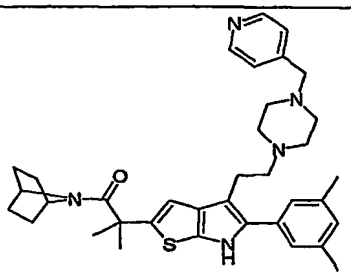
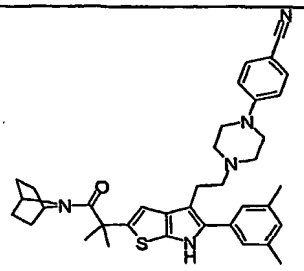
Table 3

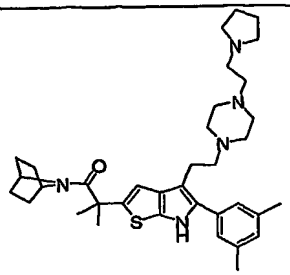
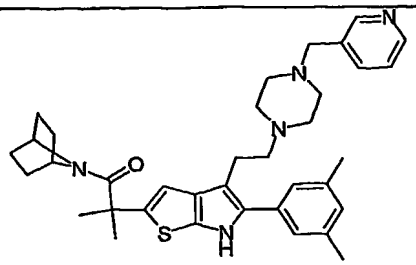
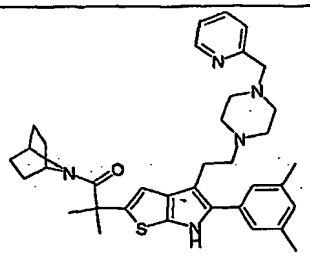
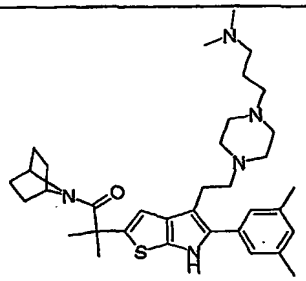
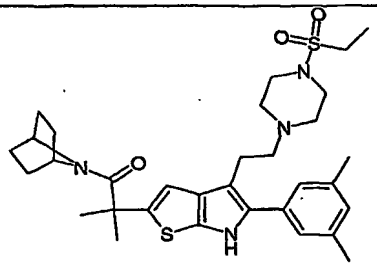
Example		MS-ESI
2.1		519 $[M+H]^+$

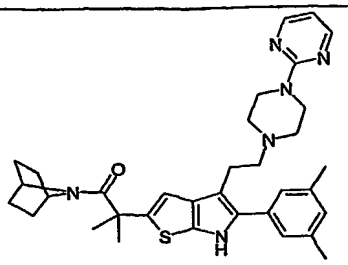
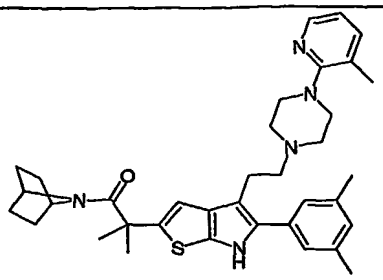
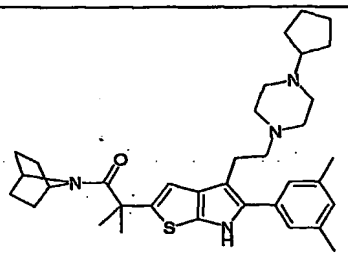
Example		MS-ESI
2.2		570 $[M+H]^+$
2.3		521 $[M+H]^+$
2.4		493 $[M+H]^+$
2.5		556 $[M+H]^+$
2.6		576 $[M+H]^+$
2.7		561 $[M+H]^+$

Example		MS-ESI
2.8		619 $[M+H]^+$
2.9		519 $[M+H]^+$
2.10		533 $[M+H]^+$
2.11		595 $[M+H]^+$
2.12		545 $[M+H]^+$
2.13		505 $[M+H]^+$

Example		MS-ESI
2.14		551 $[M+H]^+$
2.15		543 $[M+H]^+$
2.16		519 $[M+H]^+$
2.17		576 $[M+H]^+$
2.18		632 $[M+H]^+$
2.19		549 $[M+H]^+$

Example		MS-ESI
2.20		563 $[M+H]^+$
2.21		582 $[M+H]^+$
2.22		599 $[M+H]^+$
2.23		519 $[M+H]^+$
2.24		596 $[M+H]^+$
2.25		606 $[M+H]^+$

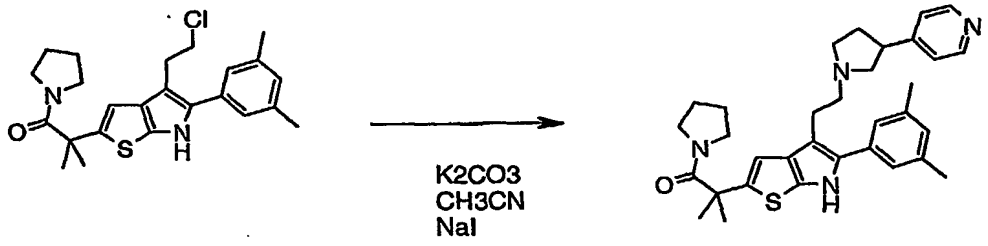
Example		MS-ESI
2.26		602 $[M+H]^+$
2.27		596 $[M+H]^+$
2.28		596 $[M+H]^+$
2.29		590 $[M+H]^+$
2.30		597 $[M+H]^+$

Example		MS-ESI
2.31		583 $[M+H]^+$
2.32		596 $[M+H]^+$
2.33		573 $[M+H]^+$

Example 2.9 was obtained by deprotection of example 2.8 in the presence of TFA in methylene chloride

Example 3

2-(1,1-dimethyl-2-oxo-2-pyrrolidin-1-ylethyl)-5-(3,5-dimethylphenyl)-4-[2-(3-pyridin-4-ylpyrrolidin-1-yl)ethyl]-6*H*-thieno[2,3-*b*]pyrrole



18

Example 3

A mixture of **18** (0.3 g; 0.7 mmol), 4-pyrrolidin-3-yl pyridine (0.31 g, 2.1 mmol), K_2CO_3 (0.29 g; 2.1 mmol) and NaI (0.314 g; 2.1 mmol) in acetonitrile (10 ml) was heated at 70°C under argon atmosphere for 20 hours. The mixture was extracted with CH_2Cl_2 and the organic layer was evaporated and purified by flash chromatography eluting with a gradient 5-10 % MeOH / CH_2Cl_2 to give **Example 3** as a solid.

Yield: 40 %

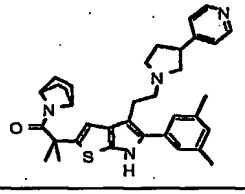
MS-ESI: 541 $[M+H]^+$

^1H NMR ($CDCl_3$) : 1.63 (s, 6H) ; 1.6-1.75 (br m, 4H) ; 1.75-1.95 (m br, 1H) ; 2.31 (s, 6H) ; 2.3-2.35 (br m, 1H) ; 2.58 (m, 1H) ; 2.7-3.2 (m, 9H) ; 3.25-3.35 (m, 1H) ; 3.4-3.6 (m, 2H) ; 6.74 (s, 1H) ; 6.91 (s, 1H) ; 7.05 (s, 2H) ; 7.15 (d, 2H) ; 8.46 (d, 2H) ; 8.53 (s, 1H).

Examples 3.1

Following a procedure similar to that described in example 3, example 3.1 were prepared.

Table 3

Example		MS-ESI
3.1		567 $[M+H]^+$

THERAPEUTIC USES

Compounds of Formula (I) are provided as medicaments for antagonising gonadotropin releasing hormone (GnRH) activity in a patient, eg, in men and/or women. To this end, a compound of Formula (I) can be provided as part of a pharmaceutical formulation which also includes a pharmaceutically acceptable diluent or carrier (eg, water). The formulation may be in the form of tablets, capsules, granules, powders, syrups, emulsions (eg, lipid emulsions), suppositories, ointments, creams, drops, suspensions (eg, aqueous or oily suspensions) or solutions (eg, aqueous or oily solutions). If desired, the formulation may include one or more additional substances independently selected from stabilising agents, wetting agents, emulsifying agents, buffers, lactose, sialic acid, magnesium stearate, terra

alba, sucrose, corn starch, talc, gelatin, agar, pectin, peanut oil, olive oil, cacao butter and ethylene glycol.

The compound is preferably orally administered to a patient, but other routes of administration are possible, such as parenteral or rectal administration. For intravenous, subcutaneous or intramuscular administration, the patient may receive a daily dose of 0.1mgkg^{-1} to 30mgkg^{-1} (preferably, 5mgkg^{-1} to 20mgkg^{-1}) of the compound, the compound being administered 1 to 4 times per day. The intravenous, subcutaneous and intramuscular dose may be given by means of a bolus injection. Alternatively, the intravenous dose may be given by continuous infusion over a period of time. Alternatively, the patient may receive a daily oral dose which is approximately equivalent to the daily parenteral dose, the composition being administered 1 to 4 times per day. A suitable pharmaceutical formulation is one suitable for oral administration in unit dosage form, for example as a tablet or capsule, which contains between 10mg and 1g (preferably, 100 mg and 1g) of the compound of the invention.

Buffers, pharmaceutically acceptable co-solvents (eg, polyethylene glycol, propylene glycol, glycerol or EtOH) or complexing agents such as hydroxy-propyl β cyclodextrin may be used to aid formulation.

One aspect of the invention relates to the use of compounds according to the invention for reducing the secretion of LH and/or FSH by the pituitary gland of a patient. In this respect, the reduction may be by way of a reduction in biosynthesis of the LH and FSH and/or a reduction in the release of LH and FSH by the pituitary gland. Thus, compounds according to the invention can be used for therapeutically treating and/or preventing a sex hormone related condition in the patient. By "preventing" we mean reducing the patient's risk of contracting the condition. By "treating" we mean eradicating the condition or reducing its severity in the patient. Examples of sex hormone related conditions are: a sex hormone dependent cancer, benign prostatic hypertrophy, myoma of the uterus, endometriosis, polycystic ovarian disease, uterine fibroids, prostatauxe, myoma uteri, hirsutism and precocious puberty. Examples of sex hormone dependent cancers are: prostatic cancer, uterine cancer, breast cancer and pituitary gonadotrophe adenoma.

The compounds of the invention may be used in combination with other drugs and therapies used to treat / prevent sex-hormone related conditions.

If formulated as a fixed dose such combination products employ the compounds of this invention within the dosage range described herein and the other pharmaceutically-active

agent within its approved dosage range. Sequential use is contemplated when a combination formulation is inappropriate.

In the field of medical oncology examples of such combinations include combinations with the following categories of therapeutic agent:

i) anti-angiogenic agents (for example linomide, inhibitors of integrin αvβ3 function, angiostatin, endostatin, razoxin, thalidomide) and including vascular endothelial growth factor (VEGF) receptor tyrosine kinase inhibitors (RTKIs) (for example those described in international patent applications publication nos. WO-97/22596, WO-97/30035, WO-97/32856 and WO-98/13354, the entire disclosure of which documents is incorporated herein by reference);

ii) cytostatic agents such as anti-oestrogens (for example tamoxifen, toremifene, raloxifene, droloxifene, iodoxyfene), progestogens (for example megestrol acetate), aromatase inhibitors (for example anastrozole, letrozole, vorazole, exemestane), anti-progestogens, anti-androgens (for example flutamide, nilutamide, bicalutamide, cyproterone acetate), inhibitors of testosterone 5α-dihydroreductase (for example finasteride), anti-invasion agents (for example metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function) and inhibitors of growth factor function, (such growth factors include for example epidermal growth factor (EGF), platelet derived growth factor and hepatocyte growth factor such inhibitors include growth factor antibodies, growth factor receptor antibodies, tyrosine kinase inhibitors and serine/threonine kinase inhibitors);

iii) biological response modifiers (for example interferon);

iv) antibodies (for example edrecolomab); and

v) anti-proliferative/anti-neoplastic drugs and combinations thereof, as used in medical oncology, such as anti-metabolites (for example anti-folates like methotrexate, fluoropyrimidines like 5-fluorouracil, purine and adenosine analogues, cytosine arabinoside); anti-tumour antibiotics (for example anthracyclines like doxorubicin, daunomycin, epirubicin and idarubicin, mitomycin-C, dactinomycin, mithramycin); platinum derivatives (for example cisplatin, carboplatin); alkylating agents (for example nitrogen mustard, melphalan, chlorambucil, busulphan, cyclophosphamide, ifosfamide, nitrosoureas, thiotepa); anti-mitotic agents (for example vinca alkaloids like vincristine and taxoids like taxol, taxotere); enzymes (for example asparaginase); thymidylate synthase inhibitors (for example raltitrexed);

topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan, irinotecan).

The compounds of the invention may also be used in combination with surgery or radiotherapy.

ASSAYS

The ability of compounds according to the invention to act as antagonists of GnRH can be determined using the following in vitro assays.

Binding Assay Using Rat pituitary GnRH Receptor

The assay is performed as follows:-

1. Incubate crude plasma membranes prepared from rat pituitary tissues in a Tris.HCl buffer (pH. 7.5, 50 mM) containing bovine serum albumin (0.1%), [I-125]D-t-Bu-Ser6-Pro9-ethyl amide-GnRH, and the test compound. Incubation is at 4°C for 90 minutes to 2 hours.
2. Rapidly filter and repeatedly wash through a glass fibre filter.
3. Determine the radioactivity of membrane bound radio-ligands using a gamma counter.

From this data, the IC_{50} of the test compound can be determined as the concentration of the compound required to inhibit radio-ligand binding to GnRH receptors by 50%. Compounds according to the present invention have activity at a concentration from 1nM to 5 μM.

Binding Assay Using Human GnRH Receptor

Crude membranes prepared from CHO cells expressing human GnRH receptors are sources for the GnRH receptor. The binding activity of compounds according to the invention can be determined as an IC_{50} which is the compound concentration required to inhibit the specific binding of [^{125}I]buserelin to GnRH receptors by 50%. [^{125}I]Buserelin (a peptide GnRH analogue) is used here as a radiolabelled ligand of the receptor.

Assay to Determine Inhibition of LH release

The LH release assay can be used to demonstrate antagonist activity of compounds, as demonstrated by a reduction in GnRH-induced LH release.

Preparation of Pituitary Glands

Pituitary glands obtained from rats are prepared as follows. Suitable rats are Wistar male rats (150-200g) which have been maintained at a constant temperature (eg, 25°C) on a 12 hour light/12 hour dark cycle. The rats are sacrificed by decapitation before the pituitary glands are aseptically removed to tube containing Hank's Balanced Salt Solution (HBSS). The glands are further processed by:-

1. Centrifugation at 250 x g for 5 minutes;
2. Aspiration of the HBSS solution;
3. Transfer of the glands to a petri dish before mincing with a scalpel;
4. Transfer of the minced tissue to a centrifuge tube by suspending the tissue three successive times in 10 ml aliquots of HBSS containing 0.2% collagenase and 0.2% hyaluronidase;
5. Cell dispersion by gentle stirring of the tissue suspension while the tube is kept in a water bath at 37°C;
6. Aspiration 20 to 30 times using a pipette, undigested pituitary fragments being allowed to settle for 3 to 5 minutes;
7. Aspiration of the suspended cells followed by centrifugation at 1200 x g for 5 minutes;
8. Re-suspension of the cells in culture medium of DMEM containing 0.37% $NaHCO_3$, 10% horse serum, 2.5% foetal bovine serum, 1% non essential amino acids, 1% glutamine and 0.1% gentamycin;
9. Treatment of the undigested pituitary fragments 3 times with 30 ml aliquots of the collagenase and hyaluronidase;
10. Pooling of the cell suspensions and dilution to a concentration of 3×10^5 cells/ml;
11. Placing of 1.0ml of this suspension in each of a 24 well tray, with the cells being maintained in a humidified 5% CO_2/95% air atmosphere at 37°C for 3 to 4 days

Testing of Compounds

The test compound is dissolved in DMSO to a final concentration of 0.5% in the incubation medium.

1.5 hours prior to the assay, the cells are washed three times with DMEM containing 0.37% $NaHCO_3$, 10% horse serum, 2.5% foetal bovine serum, 1% non essential amino acids

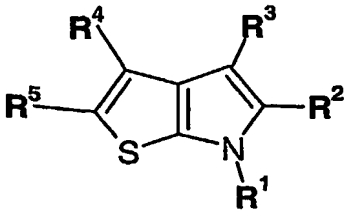
(100X), 1% glutamine (100X), 1% penicillin/streptomycin (10,000 units of each per ml) and 25 mM HEPES at pH 7.4. Immediately prior to the assay, the cells are again washed twice in this medium .

Following this, 1ml of fresh medium containing the test compound and 2nM GnRH is added to two wells. For other test compounds (where it is desired to test more than one compound), these are added to other respective duplicate wells. Incubation is then carried out at 37°C for three hours.

Following incubation, each well is analysed by removing the medium from the well and centrifuging the medium at 2000 x g for 15 minutes to remove any cellular material. The supernatant is removed and assayed for LH content using a double antibody radio-immuno assay. Comparison with a suitable control (no test compound) is used to determine whether the test compound reduces LH release. Compounds according to the present invention have activity at a concentration from 1nM to 5 μM.

CLAIMS:

1. A compound of Formula (I),



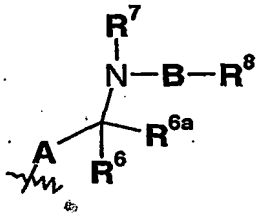
Formula (I)

wherein

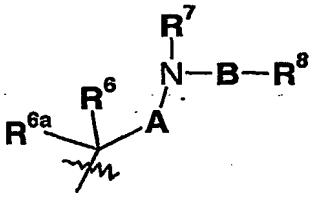
R^1 is selected from: hydrogen, optionally-substituted C_{1-6}alkyl, optionally substituted C_{1-6}alkanoyl, optionally substituted aryl or optionally-substituted arylC_{1-6}alkyl;

R^2 is an optionally-substituted mono or bi-cyclic aromatic ring;

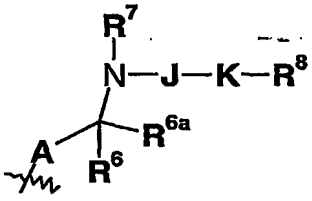
R^3 is selected from a group of Formula (IIa) to Formula (IIf):



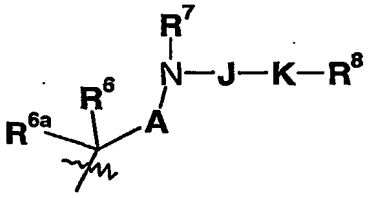
Formula (IIa)



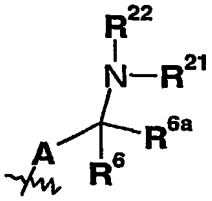
Formula (IIb)



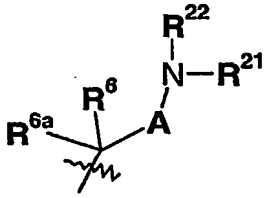
Formula (IIc)



Formula (IId)



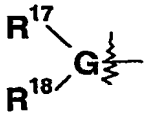
Formula (IIe)



Formula (IIf)

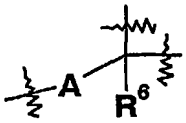
R^4 is selected from: hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted aryl, C_{1-3}perfluoroalkyl, cyano, nitro, halo, $R^9O(CH_2)_m$-, $R^9C(O)N(R^{10})$-, $R^9R^{10}NC(O)N(R^{10})$-, $R^9S(O_n)$- or $R^9R^{10}NC(O)$-$(CR^9R^{10})_t$-;

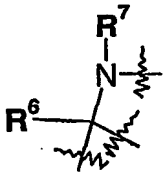
R^5 is a group of Formula (III):



Formula (III)

R^6 and R^{6a} are independently selected from hydrogen, optionally substituted C_{1-6}alkyl, optionally-substituted aryl or optionally substituted arylC_{1-6}alkyl, or R^6 and R^{6a} taken together and the carbon atom to which they are attached form a carbocyclic ring of 3-7 atoms, or R^6 and R^{6a} taken together and the carbon atom to which they are attached form a carbonyl group;

or when **A** is not a direct bond the group  forms a carbocyclic ring of 3-7 carbon atoms or a heterocyclic ring containing one or more heteroatoms;



or the group forms a heterocyclic ring containing 3-7 carbon atoms and one or more heteroatoms;

R^7 is selected from: hydrogen, optionally-substituted C_{1-6}alkyl, optionally-substituted arylC_{1-6}alkyl, optionally-substituted aryl, optionally substituted heterocyclyl, optionally substituted heterocyclylC_{1-6}alkyl, R^9OC_{1-6}alkyl-, $R^9R^{10}NC_{1-6}$alkyl-, $R^9R^{10}NC(O)C_{1-6}$alkyl, -$C(NR^9R^{10})$=NH;

or when R^3 is a group of Formula (IIc) or (IId) R^7 is of the formula –**J**-**K**-R^8;

R^8 is selected from:

(vii) hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, haloC_{1-6}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxy, hydroxyC_{1-6}alkyl, cyano, N-C_{1-4}alkylamino, N,N-di-C_{1-4}alkylamino, C_{1-6}alkyl–$S(O_n)$-, -O-R^b, –NR^bR^c, –C(O)-R^b, –C(O)O-R^b, -$CONR^bR^c$ or NH-C(O)-R^b,

where R^b and R^c are independently selected from hydrogen and C_{1-4}alkyl optionally substituted with hydroxy, amino, N-C_{1-4}alkylamino, N,N-di-C_{1-4}alkylamino, HO-C_{2-4}alkyl-NH- or HO-C_{2-4}alkyl-N(C_{1-4}alkyl)-;

(viii) nitro when **B** is a group of Formula (IV) and **X** is CH and **p** is 0;

(ix) C_{3-7}cycloalkyl, aryl or arylC_{1-6}alkyl each of which is optionally substituted by R^{12}, R^{13} and R^{14};

(x) -(Q)-aryl , -(Q)-heterocyclyl, -aryl-(Q)-aryl, each of which is optionally substituted by R^{12}, R^{13} and R^{14}

wherein -(Q)- is selected from E, F or a direct bond;

(xi) heterocyclyl or heterocyclylC_{1-6}alkyl each of which is optionally substituted by R^{12}, R^{13} and R^{14};

(xii) a group selected from R^{12}, R^{13} and R^{14};

R^9 and R^{10} are independently selected from: hydrogen, hydroxy, optionally substituted C_{1-6}alkyl, optionally substituted aryl, optionally substituted arylC_{1-6}alkyl, an optionally substituted carbocyclic ring of 3-7 atoms, optionally substituted heterocyclyl, optionally substituted heterocyclylC_{1-6}alkyl or R^9 and R^{10} taken together can form an optionally substituted ring of 3-9 atoms or R^9 and R^{10} taken together with the carbon atom to which they are attached form a carbonyl group;

R^{11} is selected from: hydrogen, optionally substituted C_{1-6}alkyl, or $N(R^9R^{10})$;

R^{12} is selected from: hydrogen, hydroxy, $R^{17}R^{18}N$-, optionally substituted C_{1-6}alkyl-$SO_2N(R^9)$-, optionally substituted aryl-$SO_2N(R^9)$-, C_{1-3}perfluoroalkyl-$SO_2N(R^9)$-; optionally substituted C_{1-6}alkyl-$N(R^9)SO_2$-, optionally substituted aryl-$N(R^9)SO_2$-, C_{1-3}perfluoroalkyl-$N(R^9)SO_2$- optionally substituted C_{1-6}alkanoyl-$N(R^9)SO_2$-; optionally substituted aryl-$C(O)N(R^9)SO_2$-, optionally substituted C_{1-6}alkyl-$S(O_n)$ -, optionally substituted aryl-$S(O_n)$ - , C_{1-3}perfluoroalkyl-, C_{1-3}perfluoroalkoxy, optionally substituted C_{1-6}alkoxy, carboxy, halo, nitro or cyano;

R^{13} and R^{14} are independently selected from: hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted C_{2-6}alkenyl, cyano, nitro, C_{1-3}perfluoroalkyl-, C_{1-3}perfluoroalkoxy, optionally substituted aryl, optionally substituted arylC_{1-6}alkyl, $R^9O(CH_2)_s$-, $R^9(O)O(CH_2)_s$-, $R^9OC(O)(CH_2)_s$-, $R^{16}S(O_n)(CH_2)_s$-, $R^9R^{10}NC(O)(CH_2)_s$- or halo;

R^{15} is selected from: hydrogen, optionally substituted C_{1-6}alkyl, $R^{19}OC(O)$-, $R^9R^{10}NC(O)$-, $R^9C(O)$-, $R^9S(O_n)$-;

R^{16} is selected from: hydrogen, C_{1-6}alkyl, C_{1-3}perfluoroalkyl or optionally-substituted aryl;

R^{17} is independently selected from: hydrogen, hydroxy, cyano or optionally substituted C_{1-6}alkyl;

R^{18} is a group of formula R^{18a}-$C(R^9R^{10})_{0-1}$- wherein R^{18a} is selected from: $R^{19}OC(O)$-, $R^9R^{10}NC(O)$-, $R^9R^{10}N$-, $R^9C(O)$-, $R^9C(O)N(R^{10})$-, $R^9R^{10}NC(O)$-, $R^9R^{10}NC(O)N(R^{10})$-, $R^9SO_2N(R^{10})$-, $R^9R^{10}NSO_2N(R^{10})$-, $R^9C(O)O$-, $R^9OC(O)$-, $R^9R^{10}NC(O)O$-, R^9O-, $R^9S(O_n)$-, $R^9R^{10}NS(O_n)$ -, optionally substituted C_{1-6}alkyl, optionally substituted heterocyclyl;

or R^{17} and R^{18} when taken together form an optionally substituted carbocyclic ring of 3-7 atoms or optionally substituted heterocyclyl;

R^{19} is selected from: hydrogen, optionally substituted C_{1-6}alky, optionally substituted aryl, optionally substituted arylC_{1-6}alkyl, optionally substituted C_{3-7}cycloalkyl, optionally substituted heterocyclyl or optionally substituted heterocyclylC_{1-6}alkyl;

R^{20} is selected from R^{12} or R^{13};

R^{21} and R^{22} are independently selected from hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-7}cycloalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylC_{1-6}alkyl, optionally substituted C_{3-6}alkenyl, optionally substituted C_{3-6}alkynyl, -$(C_{1-5}$alkyl$)_{aa}$-$S(O_n)$-$(C_{1-5}$alkyl$)_{bb}$-; $R^9R^{10}NC_{2-6}$alkyl, R^9OC_{2-6}alkyl or $R^9R^{10}NC(O)C_{2-6}$alkyl, with the proviso that R^9 and R^{10} independently or taken together are not optionally substituted aryl or optionally substituted arylC_{1-6}alkyl; or

R^{21} and R^{22} taken together form an optionally substituted non-aromatic heterocyclic ring;

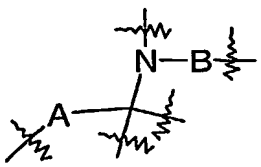
A is selected from:

(v) a direct bond;

(vi) optionally-substituted C_{1-5}alkylene wherein the optional substituents are independently selected from: optionally-substituted C_{1-6}alkyl optionally-substituted aryl, optionally substituted arylC_{1-6}alkyl or substituted arylC_{1-6}alkyl;

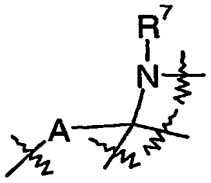
(vii) a carbocyclic ring of 3-7 atoms;

(viii) a carbonyl group;

or when R^3 is a group of Formula (IIa) or (IIb), the group 

forms a heterocyclic ring containing 3-7 carbon atoms and one or more heteroatoms;

or when $\mathbf{R^3}$ is a group of Formula (IIa), (IIb), (IIc) or (IId), the group

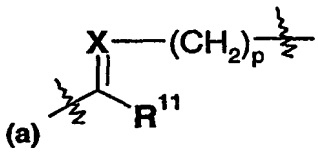


forms a heterocyclic ring containing 3-7 carbon atoms and one or more heteroatoms;

B is selected from:

(i) a direct bond;

(ii) a group of Formula (IV)



Formula (IV)

wherein:

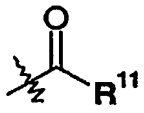
X is selected from N, CH or a saturated heterocyclic ring,

wherein at position (a) Formula (IV) is attached to the nitrogen atom and the $(CH_2)p$ group is attached to $\mathbf{R^8}$; and

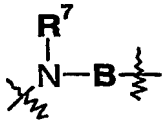
(iii) a group independently selected from: optionally substituted $C_{1\text{-}6}$alkylene, optionally substitute $C_{3\text{-}7}$cycloalkyl, optionally substituted $C_{3\text{-}6}$alkenylene, optionally substituted $C_{3\text{-}6}$alkynyl, $C_{1\text{-}6}$alkoxy, $(C_{1\text{-}5}alkyl)_{aa}$-$S(O_n)$-$(C_{1\text{-}5}alkyl)_{bb}$-, $(C_{1\text{-}5}alkyl)_{aa}$-O-$(C_{1\text{-}5}alkyl)_{bb}$- or $(C_{1\text{-}5}alkyl)_{aa}$-$N(\mathbf{R^{15}})$- $(C_{1\text{-}5}alkyl)_{bb}$,

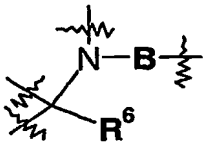
wherein $\mathbf{R^{15}}$ and the $(C_{1\text{-}5}alkyl)_{aa}$ or $(C_{1\text{-}5}alkyl)_{bb}$ chain can be joined to form a ring;

or the group $-\mathbf{B}\text{-}\mathbf{R^8}$ represents a group of Formula (V)



Formula (V);

or the group  together forms a heterocylic ring containing 5-7 carbons atoms;

or the group  forms a heterocyclic ring containing 3-7 carbon atoms and one or more heteroatoms;

E is –O-, -S(O_n), -C(O)-, -NR^{15}- or -C(R^9R^{10})$_q$;

F is -E(CH_2)$_r$- or -(CH_2)$_r$E -;

G is selected from: hydrogen, halo, CN, NO_2, N, O, S(O_n), C(O), C(R^9R^{10})$_t$, optionally substituted C_{2-6}akenylene, optionally substituted C_{2-6}alkynylene, optionally substituted heterocyclyl or a direct bond to R^{18},

J is a group of the formula: -(CH_2)$_s$-**L**-(CH_2)$_s$- wherein when **s** is greater than 0, the alkylene group is optionally substituted

K is selected from: a direct bond, -O-(CH_2)$_s$-, -C(O)-(CH_2)$_s$- , -S(O_n) -(CH_2)$_s$-, -N(R^{18})-(CH_2)$_s$-, -OC(O)-(CH_2)$_s$-, -C(O)O-(CH_2)$_s$-, -OS(O_n)-(CH_2)$_s$-, or -S(O_n)-O-(CH_2)$_s$-;

L is selected from optionally substituted aryl or optionally substituted heterocyclyl;

n is an integer between 0 and 2;

p is an integer between 0 and 4;

q is an integer between 0 and 4;

r is an integer between 0 and 4;

s is an integer between 0 and 4; and

t is an integer between 0 and 4;

aa and **bb** are independently selected from 0 or 1

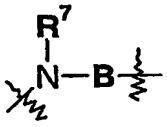
with the proviso that

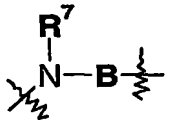
(iii) when **G** is hydrogen, halo, CN or NO_2 then R^{17} and R^{18} are both absent;

(iv) when **G** is O, S(O_n), C(O) or C($R^{11}R^{12}$)$_t$ then **G** is substituted by a single group independently selected from the definition of R^{17} or R^{18} and when G is a direct bond to R^{18} then **G** is substituted by a single group selected from R^{18}; and

or a salt, pro-drug or solvate thereof.

2. A compound according to Claim 1 wherein R^3 is selected from a group of Formula (IIa) or Formula (IIb).

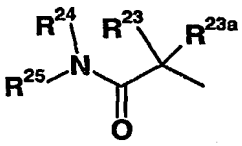
3. A compound according to Claim 2 wherein **B** is optionally substituted C_{1-6}alkylene or the group  forms a C_{5-7}heterocyclic ring.

4. A compound according to Claim 3 wherein the group  forms piperazinyl.

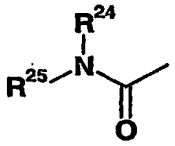
5. A compound according to any one of Claims 2, 3, 4 or 5 wherein $\mathbf{R^8}$ is selected from C_{3-7}cycloalkyl, aryl, arylC_{1-6}alkyl heterocyclyl or heterocyclylC_{1-6}alkyl each of which is optionally substituted by $\mathbf{R^{12}}$, $\mathbf{R^{13}}$ and $\mathbf{R^{14}}$.

6. A compound according to Claim 5 wherein $\mathbf{R^8}$ is selected from: pyridyl, thiazolyl, pyrrolidinyl, phenyl and benzyl

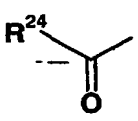
7. A compound according to any one of the preceding claims wherein $\mathbf{R^5}$ is a group of Formula (III) wherein the group of Formula (III) is selected from one of **III-a** to **III-j**;



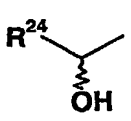
III-a



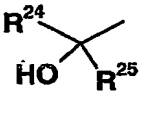
III-b



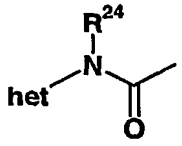
III-c



III-d

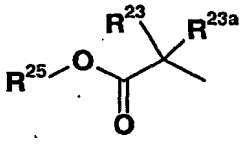


III-e

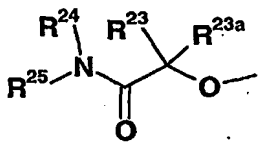


III-f

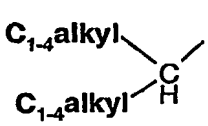
III-g



III-h



III-i



III-j

wherein:

het represents an optionally substituted 3- to 8- membered heterocyclic ring containing from 1 to 4 heteroatoms independently selected from O, N and S;

$\mathbf{R^{23}}$ and $\mathbf{R^{23a}}$ are independently selected from hydrogen or optionally substituted C_{1-8}alkyl; or $\mathbf{R^{23}}$ and $\mathbf{R^{23a}}$ together with the carbon to which they are attached form an optionally substituted 3 to 7-membered cycloalkyl ring

R^{24} is selected from hydrogen, optionally substituted C_{1-8}alkyl, optionally substituted aryl, -R^d-Ar, where R^d represents C_{1-8}alkylene and Ar represents optionally substituted aryl, and optionally substituted 3- to 8- membered heterocyclic ring optionally containing from 1 to 3 further heteroatoms independently selected from O, N and S;

R^{25} is selected from hydrogen; optionally substituted C_{1-8}alkyl and optionally substituted aryl;

or where the group of Formula (III) represents a group of Formula **III-a** , **III-b** or **III-i**, then the group $NR^{24}(-R^{25})$ represents an optionally substituted 3- to 8- membered heterocyclic ring optionally containing from 1 to 3 further heteroatoms independently selected from O, N and S;

or where the group of Formula (III) represents structure **III-e**, R^{24} and R^{25} together with the carbon to which they are attached represents an optionally substituted 3- to 8- membered heterocyclic ring optionally containing from 1 to 4 heteroatoms independently selected from O, N and S;

8. A compound according to any one of the preceding claims wherein R^2 is selected from an optionally substituted monocyclic aromatic ring structure wherein the optional substituents are selected from cyano, NR^eR^f, optionally substituted C_{1-8}alkyl, optionally substituted C_{1-8}alkoxy or halo wherein R^e and R^f are independently selected from hydrogen, C_{1-6}alkyl or aryl.

9. A compound according to any one of the preceding claims wherein R^1 is hydrogen.

10. A compound selected from:

N-{2-[2-(1,1-dimethyl-2-oxo-2-pyrrolidin-1-ylethyl)-5-(3,5-dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrol-4-yl]ethyl}-4-pyridin-4-ylbutan-1-amine;

N-{2-[2-[2-(7-azabicyclo[2.2.1]hept-7-yl)-1,1-dimethyl-2-oxoethyl]-5-(3,5-dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrol-4-yl]ethyl}-4-pyridin-4-ylbutan-1-amine;

N-{2-[2-[2-(7-azabicyclo[2.2.1]hept-7-yl)-1,1-dimethyl-2-oxoethyl]-5-(3,5-dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrol-4-yl]ethyl}-4-pyridin-4-ylethyl-1-amine;

{(2*S*)-2-[2-[2-(7-azabicyclo[2.2.1]hept-7-yl)-1,1-dimethyl-2-oxoethyl]-5-(3,5-dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrol-4-yl]propyl}(2-pyridin-4-ylethyl)amine;

N-{2-[2-[2-(2-azabicyclo[2.2.2]oct-2-yl)-1,1-dimethyl-2-oxoethyl]-5-(3,5-dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrol-4-yl]ethyl}-4-pyridin-4-ylbutan-1-amine;

N-{2-[2-[2-(2-azabicyclo[2.2.2]oct-2-yl)-1,1-dimethyl-2-oxoethyl]-5-(3,5-dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrol-4-yl]ethyl}-4-pyridin-4-ylethyl-1-amine;

{(2*S*)-2-[2-[2-(2-azabicyclo[2.2.2]oct-2-yl)-1,1-dimethyl-2-oxoethyl]-5-(3,5-dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrol-4-yl]propyl}(2-pyridin-4-ylethyl)amine;

2-(1,1-dimethyl-2-oxo-2-pyrrolidin-1-ylethyl)-5-(3,5-dimethylphenyl)-4-{2-[4-(pyridin-4-ylmethyl)piperazin-1-yl]ethyl}-6*H*-thieno[2,3-*b*]pyrrole;

2-(1,1-dimethyl-2-oxo-2-pyrrolidin-1-ylethyl)-5-(3,5-dimethylphenyl)-4-{2-[4-(pyridin-2-ylmethyl)piperazin-1-yl]ethyl}-6*H*-thieno[2,3-*b*]pyrrole;

2-(1,1-dimethyl-2-oxo-2-pyrrolidin-1-ylethyl)-5-(3,5-dimethylphenyl)-4-{2-[4-methylpiperazin-1-yl]ethyl}-6*H*-thieno[2,3-*b*]pyrrole;

2-(1,1-dimethyl-2-oxo-2-pyrrolidin-1-ylethyl)-5-(3,5-dimethylphenyl)-4-{2-[4-(pyridin-4-yl)piperazin-1-yl]ethyl}-6*H*-thieno[2,3-*b*]pyrrole;

2-[2-(2-azabicyclo[2.2.2]oct-2-yl)-1,1-dimethyl-2-oxoethyl]-5-(3,5-dimethylphenyl)-4-[2-(4-methylpiperazin-1-yl)ethyl]-6*H*-thieno[2,3-*b*]pyrrole;

4-[2-(4-allylpiperazin-1-yl)ethyl]-2-[2-(7-azabicyclo[2.2.1]hept-7-yl)-1,1-dimethyl-2-oxoethyl]-5-(3,5-dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrole;

2-[2-(7-azabicyclo[2.2.1]hept-7-yl)-1,1-dimethyl-2-oxoethyl]-5-(3,5-dimethylphenyl)-4-{2-[4-(2-morpholin-4-yl-2-oxoethyl)piperazin-1-yl]ethyl}-6*H*-thieno[2,3-*b*]pyrrole; and

2-[2-(7-azabicyclo[2.2.1]hept-7-yl)-1,1-dimethyl-2-oxoethyl]-5-(3,5-dimethylphenyl)-4-{2-[4-(pyridin-4-ylmethyl)piperazin-1-yl]ethyl}-6*H*-thieno[2,3-*b*]pyrrole;

or a salt, pro-drug or solvate thereof.

11. A compound, or salt, pro-drug or solvate thereof, according to any one of Claims 1 to 10 for use as a medicament.

12. A pharmaceutical formulation comprising a compound, or salt, pro-drug or solvate thereof, according to any one of Claims 1 to 10 and a pharmaceutically acceptable diluent or carrier.

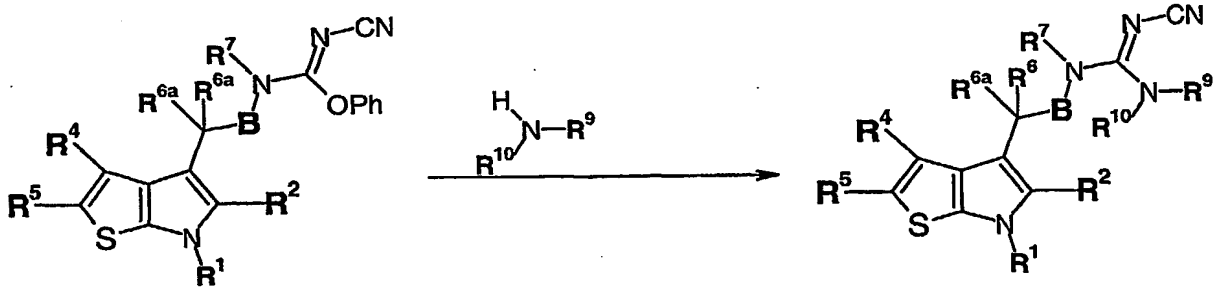
13. Use of a compound, or salt, pro-drug or solvate thereof, according to any one of Claims 1 to 10, in the manufacture of a medicament for antagonising gonadotropin releasing hormone activity.

14. Use of a compound, or salt, pro-drug or solvate thereof, according to any one of Claims 1 to 10, in the manufacture of a medicament for administration to a patient, for therapeutically treating and/or preventing a sex hormone related condition in the patient.

15. The use according to claim 14, wherein the sex hormone related condition is selected from a sex hormone dependent cancer, benign prostatic hypertrophy or myoma of the uterus.

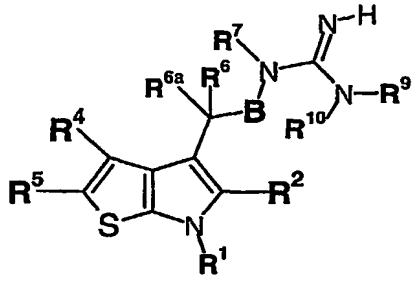
16. A process of producing a compound, or salt, pro-drug or solvate thereof, according to any one of Claims 1 to 10, wherein the process comprises a reaction step selected from any one of steps (a) to (e):-

(a) Reaction of a compound of formula **XXXII** as follows



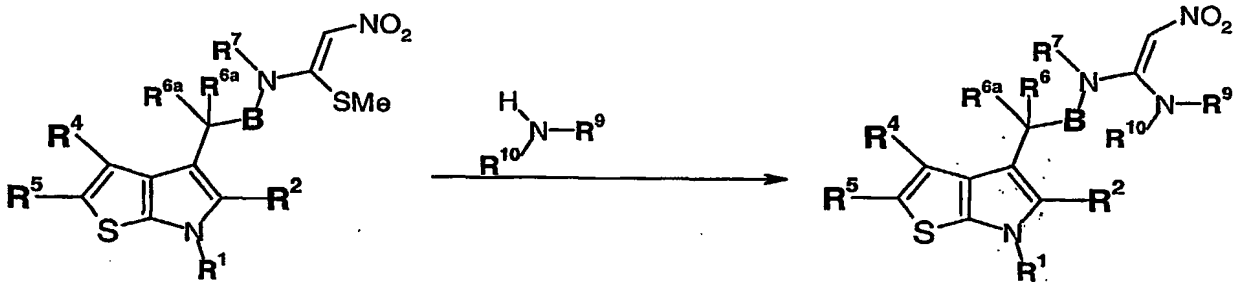
XXXII **XXXIII**

(b) Cleavage of the cyano group of a compound of formula **XXXIII** in the presence of acid to produce a compound of formula **XXXIV**



XXXIV

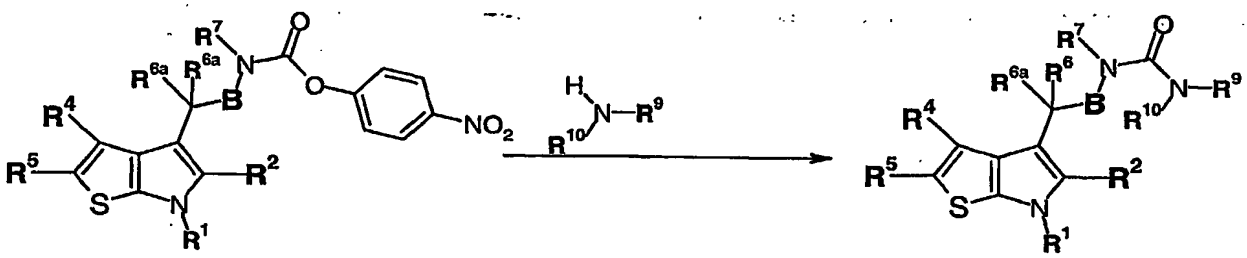
(c) Reaction of a compound of formula **XXXV** as follows



XXXV

XXXVI

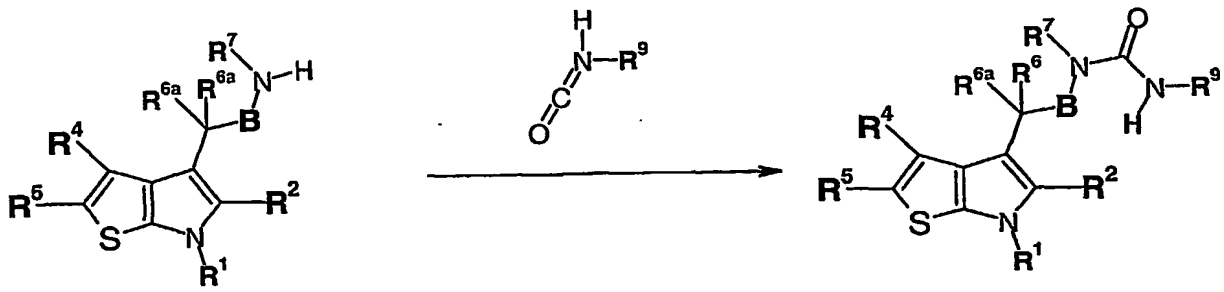
(d) Reaction of a compound of formula **XXXVII** as follows



XXXVII

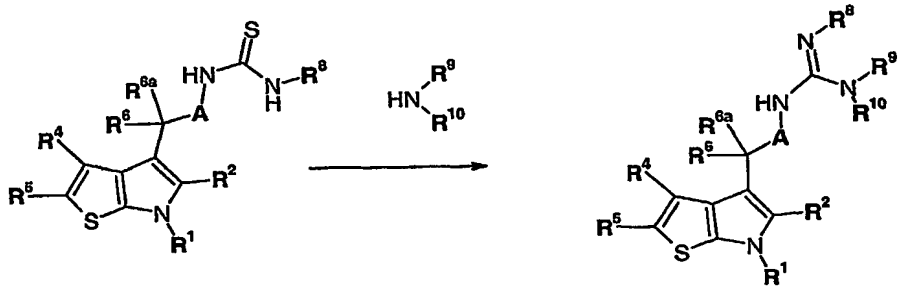
XXXVIII

(e) Reaction of a compound of formula **XXXIX** as follows



XXXIX XXXX

(f) to form a compound wherein **X** is nitrogen and Reaction of a compound of formula XXXXI as follows



XXXXI XXXXII

and thereafter if necessary:

i) converting a compound of the Formula (I) into another compound of the Formula (I);

ii) removing any protecting groups;

iii) forming a salt, pro-drug or solvate.